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Cancer Dose-Response Modeling of Low Dose Radiation Exposure

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ABSTRACT

GIZELLE SUSETTE BAKER. Cancer Dose-Response Modeling of Low Dose Radiation Exposure. (Under the direction of DAVID G. HOEL, Ph.D.).

Many late effects from exposure to ionizing radiation, including cancers, have been described in the literature. The identification and quantification of radiation-induced health effects is an important and complex issue. Recommendations for radiation safety and protection from the International Commission on Radiological Protection are made using a linear no threshold risk model on epidemiological data. A major obstacle in this process is the limited availability of data to directly measure the health effects of radiation on human populations. One way to circumvent this problem is to use experimental data from laboratory animals and extrapolate across species to man.

The cancer incidence and mortality data from the Japanese atomic bomb survivors was adjusted for uncertainty that exists in the dose estimates, systematic error in the neutron dose estimates, and a dose-dependent relative biological effectiveness. A threshold term was included in the Poisson regression model as a surrogate for nonlinearity in the dose response curve. The research suggests that the threshold improves the fit of the model for the solid tumor incidence, as well as the leukemia

incidence and mortality data (although the mortality data was not a significant improvement).

In our study, $B6CF_1$ mice were used to assess the shape of the dose response curve and the effects of fractionation at low doses. The Cox proportional hazards model was used to as an empirical model, while the two-stage clonal expansion model was used as the biologically based cancer model in which information on the carcinogenesis process is incorporated into the model. The two models resulted in similar descriptions of the dose response curves, cancer risks, neutron relative biological effectiveness and dose rate effectiveness factor associated with exposure to ionizing radiation. The analyses indicate that the dose response curve appears linear in the low dose region, and fractionation reduces the effectiveness of gamma exposure while increasing the effectiveness of neutron exposure.

1. INTRODUCTION

The derivation of cancer risks from low dose and low dose rate exposures to ionizing radiation is important in the setting of standards for radiological protection. The problem is there are only a few human populations exposed at low to moderate dose rates in which direct estimates of cancer risk can be calculated. Therefore, most of the information available today about cancer risks in human populations following exposure to ionizing radiation come from extrapolating high dose, high dose rate studies. The Japanese atomic bomb survivor Life Span Study (LSS) data is a major source of a data for determining risk estimates of radiation-induces cancers (Fry and Sinclair 1987;Vaeth and Stram 1989). The issue that arises when modeling cancer risks at low doses using epidemiological methods is that it is nearly impossible to observe, with statistical confidence an increased cancer incidence due to exposure (National Council on Radiation Protection and Measurements 2001). Since error in dosimetry impact both the risk estimates and radiation protection standards, it is important to consider them in the modeling of this data.

The radiation exposures that resulted from the two atomic bombs dropped in Japan are considered mixed exposures, since the survivors were exposed to a combination of gamma and neutron radiation. The uranium bomb used in Hiroshima generated a substantially higher dose of neutron as compared to the minimal neutrons delivered by the plutonium bomb in Nagasaki (Hollingsworth 1986;Roberts 1987). The difference in the bombs is important in that there is an inverse relationship between the risk coefficients for gamma rays and neutrons (Kellerer and Nekolla 1997). This relationship is obvious in that the excess mortality is made up of a neutron and gamma

ray component; and as the attribution due to neutrons increases the attribution of photons decreases. In previous analyses of for Radiation Effects Research Foundation (RERF) reports on the atomic bomb survivors, and for radiation protection purposes a linear dose response relationship has been assumed for low dose exposures of neutrons and photons. In recent years the possibility of non-linearities in the low dose region of the dose response curve has been a topic that has generated a lot of interest. Threshold models have been used as a surrogate for non-linearities, and in an analysis using the unadjusted dosimetry system 1986 (DS86) dose values, a threshold modeled significantly improved the fit of the model to the leukemia incidence data (Hoel and Li 1998). It was hypothesized that the improvement in fit with a threshold term could simply be the artifact of the errors associated with the dose estimates (Little 1999). Therefore, it will be important to see if the findings hold true after adjustments are made to the dose estimates.

It is recognized that both systematic errors and uncertainty in the dose estimates may alter the shape of the dose response relationship and in effect the evidence for curvature in the dose response curve. The problem with the uncertainty in the dose estimates, also known as random error in the dosimetry, has been investigated (Gilbert 1984;Jablon S. 1971) and many papers have been published on the methods that have been developed to account for random error in the total dose (Little and Muirhead 1996, 1997;Pierce et al. 1990). More recently, these methods have been modified to account for the error in the two subcomponents of the dose, gamma and neutron dose, separately (Little and Muirhead 2000;Pierce and Preston 2000). This allows for a better assessment of the contribution the neutron component of dose makes on the dose response curve, and

allows for the correction to be combined with a different relative biological effectiveness (RBE) values in calculating the weighted dose.

The issue of a systematic underestimation of the neutron dose also has an impact on the shape of the resulting dose response curve. The issue arises when looking at experimental neutron activation measurements; these indicate that there are large discrepancies between the DS86 neutron estimates and the neutron activation measurements in Hiroshima. The initial discrepancies were noticed in thermal (slow) neutron activation measurements (Straume et al. 1992) and tentative corrections were made to bring the DS86 dose estimates in line with the thermal neutron measurements. Kellerer et al. (1997) investigated the effects of adjusting the dose estimates and found that although a linear model fit the data a purely quadratic function of gamma exposure was also consistent with the data. Recent improvements in accelerator mass spectrometry have allowed for the measurement of ^{63}Ni in copper samples to determine the fast neutron fluences, which is more representative of the exposure doses (Ruhm et al. 2000). Therefore, to realistically estimate the neutron contribution, corrections should be made to bring the DS86 neutron estimates in line with the fast neutron activation measurements instead of the slow neutron activation measurements (Kellerer and Walsh 2001;National Research Council 2001).

The neutron relative biological effectiveness is the estimate of how much more efficient high-LET radiations are at causing at set biological effect compared to photons per unit of absorbed dose (Britten et al. 2001). Therefore, weighting factors, that depend on the neutron energy, have been adopted to best represent the RBE of low doses with regard to stochastic late effects (Kellerer and Nekolla 1997). In radiobiology the unit

gray (Gy) is used to represent joules per kilogram (J/kg), the individual dose measurements, and sieverts (Sv) are the unit used to represent the dose equivalent, when the difference in effectiveness (RBE) is accounted for. In the assessments of cancer risks due to radiation exposure calculated based on the atomic bomb survivor data the average dose equivalents are calculated for each stratum using a constant RBE of 10 (Pierce et al. 1996b). Radiation biology studies have shown that RBE is not a constant value; instead it varies with radiation dose, so that the larger the dose the smaller the RBE (Straume et al. 1992). The large effects of small errors in the low dose region make it important to consider all known components that effect dose estimates including a variable RBE when modeling cancer risks.

The dose-response relationship between exposure to ionizing radiation and cancer risks in humans has primarily been analyzed using Poisson regression techniques, although the use of biologically based models has gained attention in recent years (Kai et al. 1997). The model is not focused on the low dose behavior, but has provided perspective on the temporal behavior of risk after acute exposures to ionizing radiation (Little 1999). The atomic bomb data is a high dose high dose rate data set in which subjects were exposed to acute doses of mixed radiation; therefore, the information available is not sufficient to provide insight into the cancer effects of

- exposure pattern – radiation quality, low doses, low dose rates, protracted or fractionated exposures
- risk modifiers – including genetic differences as well as other factors
- dose weighting factors – relative biological effectiveness, dose rate effectiveness factor

(Cardis et al. 2001).

Knowledge gained from experimental animal studies is used supplement the information that is provided by the epidemiological data used in estimating the risks of radiation exposure on human populations. Evidence indicates that the magnitude of cancer effects varies with radiation quality, dose, dose rate, cancer endpoint, and other factors; that cannot be directly estimated from the human studies. Therefore, dose weighting factors have been calculated from *in vivo* and *in vitro* cell line studies and animal studies and are applied in risk assessment.

2. SPECIFIC AIMS

The goal of this research is to investigate the low dose region of the cancer dose response curve for exposure to ionizing radiation. The specific aims of this research are to:

1.) To compare the fits of the threshold models before and after the incorporation of the appropriate dose adjustments are made for the uncertainty in the dose estimated and systematic error in the neutron component of dose.

2.) To explore the effects of a dose dependent RBE on the shape of the dose response curve at low doses.

3.) Investigate the similarities and differences in the dose response curve and risk estimates between the empirical survivor models and biologically based survivor models.

4.) Examine the effect of exposure pattern (dose fractionation and radiation quality) on the shape of the dose-response curves for total cancer, solid tumors, and leukemias using animal data.

3. REVIEW OF LITERATURE

3.1 Dose Uncertainty Adjustment

The data available from RERF does not contain the true gamma and neutron doses (D_γ and D_n respectively), because these values are unknown; the doses available in the LSS data are nominal doses (d_γ and d_n – dose estimates) based on an elaborate dose reconstruction. Inherent in a dose reconstruction is a non-negligible amount of dose uncertainty, due to random and non-random errors in the reconstruction process (Kaul 1989). Random error in the dose estimates have been shown to alter the shape of the dose response curve (Little and Muirhead 1996;Pierce et al. 1990), and result in the incorporation of a systematic bias in the risk estimates (Little and Muirhead 2000;Pierce et al. 1992), therefore nullifying any available evidence for linearity or curvilinearity (Stram 1989).

The issue of dose uncertainty in the RERF dose estimates has been investigated, and it has been determined that the probable form and magnitude of the error follow a log-normal distribution with the coefficient of variation somewhere between 25 and 45% (Gilbert 1984;Jablon S. 1971), although in the majority of studies that account for the uncertainty in the dose estimates it is assumed to be 35%. Methods developed in Pierce

et al. (1990, 1992) use the information on the distribution of the of the uncertainty in the doses (log-normal), the assumed distribution of the true doses (Weibull) and the empirical distribution of the nominal doses in adjusting the total dose estimates ($d_\gamma + 10d_n$). The average true dose given the nominal dose (Avg[D | d]) is calculated for every cell in the data (Pierce et al. 1990, 1992) using

$$\mathrm{Avg}[D \mid d] = \sum \frac{f(D,d) \cdot D \cdot \Delta D}{\sum f(D,d) \cdot \Delta D},$$

where

$$f(D,d) = \frac{\theta_1 \theta_2 D^{(\theta_2 - 1)} \exp\{-\theta_1 D^{\theta_2}\} \cdot \exp\left\{\frac{[\log(D) - \log(d_j)]^2}{2\sigma^2}\right\}}{d_j \sigma \sqrt{2\pi}}.$$

These adjusted doses have been included in the most recent mortality data made available by RERF. When Avg[D | d] is used in place of the nominal dose so that the model so we are modeling Avg[λ(D) | d] instead of λ(D), but the estimated regression parameters (Little 2000). The problem with these corrections is that they require that the RBE be fixed at 10 and don't allow for a correction of the neutron doses. The methods developed by Pierce et al. can been generalized so that they are applied separately to the neutron and gamma components of the dose (Little and Muirhead 2000;Pierce and Preston 2000).

3.2 Systematic Error in the Neutron Dose Estimates

The DS86 was published in 1986 as the replacement for the previous dosimetry (T65D). The major change in the new dosimetry were in the neutron dose estimates in Hiroshima – the neutron doses were reduced from approximately 20% of the total dose to about 2% of the total dose while the gamma dose increased by a factor of 2 to 3.5 depending on the distance from the hypocenter (Roberts 1987). The doses in Nagasaki

were also altered, although the changes were much smaller; the gamma dose was slightly reduced and the already minimal neutron doses further reduced.

Even with these corrections in the neutron doses there still appear to be discrepancies with the more recent neutron activation measurements (Kellerer and Walsh 2001). The new measurements indicate that the neutron component of dose has been systematically underestimated for distances beyond 1 to 1.5 kilometers (Straume et al. 1992). Therefore, Straume suggests that in order to obtain more realistic estimates of the neutron contribution the neutron doses must be corrected upwards in line with the neutron activation measurements as a function of the distance from the hypocenter using the relationship

$$K' = C(r) \cdot K$$

where K′ is the corrected free in air kerma (measurement of radiation in the air), K in the uncorrected (DS86) free in air kerma, and C(r) is a correction factor that is a function of ground distance in kilometers from the hypocenter (Kellerer and Nekolla 1997). Since there is a direct relationship between free in air kerma and absorbed dose the relationship for between corrected and uncorrected dose is the same as for free in air kerma. Although the latest data on fast neutrons has not been published the relationship between the gamma and neutrons doses has been discussed (Kellerer and Walsh 2001;National Research Council 2001) and this relationship is used to calculate a tentative correction for the neutron activation measurements.

Calculating the correction factor as a function of distance introduces a problem because there is no information on distance from the hypocenter available in the data. Keller and Nekolla (1997) suggest that C(r) can be inferred from the magnitude of the

gamma component of dose, since dose and distance are related and the gamma dose is the most highly correlated dose since it is the least dependent on shielding factors.

3.3 Dose Dependent RBE

In previous analyses and reports on cancer risks based on the atomic bomb survivors it has been acknowledged that neutrons are more effective at producing the a biological effect than gamma radiation (Committee on the Biological Effects of Ionizing Radiation 1990;ICRP 1991;ICRU 1986;United Nations Scientific Committee on the Effects of Atomic Radiation 1994). In general the RBE for a given neutron dose is defined as $RBE_n(D_n) = \frac{D_\gamma}{D_n}$, where D_γ is the gamma dose required to produce the same biological effect as a given dose neutron dose (D_n) (Britten et al. 2001). Most of the current information on the neutron RBE comes from experimental animal data, not epidemiological data (Kellerer and Walsh 2001;Little 1997). Although it has been accepted in principle, that as dose decreases RBE must increase (Abrahamson 1989), it has not been incorporated in the analysis of the atomic bomb data until recently because the it cannot be calculated directly from the RERF data (Kellerer and Nekolla 1997). Therefore, in the cancer incidence and mortality reports on the atomic bomb survivors a fixed weighting factor of 10 is used in place of a dose-dependent RBE (Mabuchi et al. 1994;Preston et al. 1994;Ron et al. 1994;Thompson et al. 1994).

Radiation biology studies of chromosomal aberration in human lymphocytes (Edwards et al. 1980) suggests that the dose-independent RBE results in an overestimation of the risk associated with the neutron component of dose (Rossi and Zaider 1990;Stram et al. 1993). Rossi and Zaider (1996) have shown that using the data obtained from human lymphocyte chromosomal aberration studies a reasonable dose-

dependent RBE_n can be calculated using the linear-quadratic model for the effects of gamma rays ($\alpha_\gamma d_\gamma + \beta_\gamma d_\gamma^2$) and a simple linear model for the neutrons ($\alpha_n d_n$) (Rossi and Zaider 1996). In the event of a mixed exposure the RBEn is dependent on both the neutron and gamma doses so that the RBE is calculated as

$$RBE(d_\gamma, d_n) = \frac{\alpha_\gamma}{2\beta_\gamma d_n}\left[\sqrt{\left(1+\frac{2\beta_\gamma}{\alpha_\gamma}d_\gamma\right)^2 + \frac{4\beta_\gamma\alpha_n}{\alpha_\gamma^2}d_n} - \left(1+\frac{2\beta_\gamma}{\alpha_\gamma}d_\gamma\right)\right],$$

where $\alpha_\gamma = 1.57\times10^{-2}$ Gy^{-1}, $\beta_\gamma = 5.0\times10^{-2}$ Gy^{-2}, and $\alpha_n = 83.5\times10^{-2}$ Gy^{-1} (Edwards et al. 1980).

The Poisson regression models given in the RERF reports are easily adjusted to allow for a variable RBE with an adjustment for the dose uncertainty and the neutron correction factor corrected dose so that the total dose would be $d = d_\gamma + RBE(d_\gamma,d_n)\cdot d_n$, where the d is the $Avg[(D_\gamma + RBE(D_\gamma,D_n)\cdot D_n) \mid d_\gamma, d_n]$ and d_n is corrected in line with the neutron activation measurements. Using these methods the RBE in the data ranges from 2.3 at approximately 500 meter from the hypocenter to values as high as 53 at further distances from the hypocenter (Pierce et al. 1996a;Rossi and Zaider 1996).

3.4 Two-Stage Clonal Expansion Model

The goal of biologically based dose-response modeling is to used information obtained from basic science to inform a quantitative models of a disease process (Moolgavkar et al. 1988). Most biologically based carcinogenesis models are stochastic population models that describe the carcinogenesis process as the temporal evolution and growth of cells in several distinct stages. The two-stage clonal expansion model is the mathematical idealization of the initiation-promotion-progression theory of carcinogenesis (Moolgavkar 1986).

In order to apply the two-stage clonal expansion model many assumption must be made about the cells, their behavior in the different stages and the endpoint of interest. It is assumed that at any given time in the study period there is a large, constant number of somatic cells (X_0) that are susceptible to genetic transformation, the initiated cells (($X_1(t)$) reproduce in a stochastic manner , and that once a malignant cell ($X_2(t)$) is formed it will inevitably become an observable tumor (Kopp-Schneider et al. 1994;Nakamura and Hoel 2002;Sherman and Portier 1997).

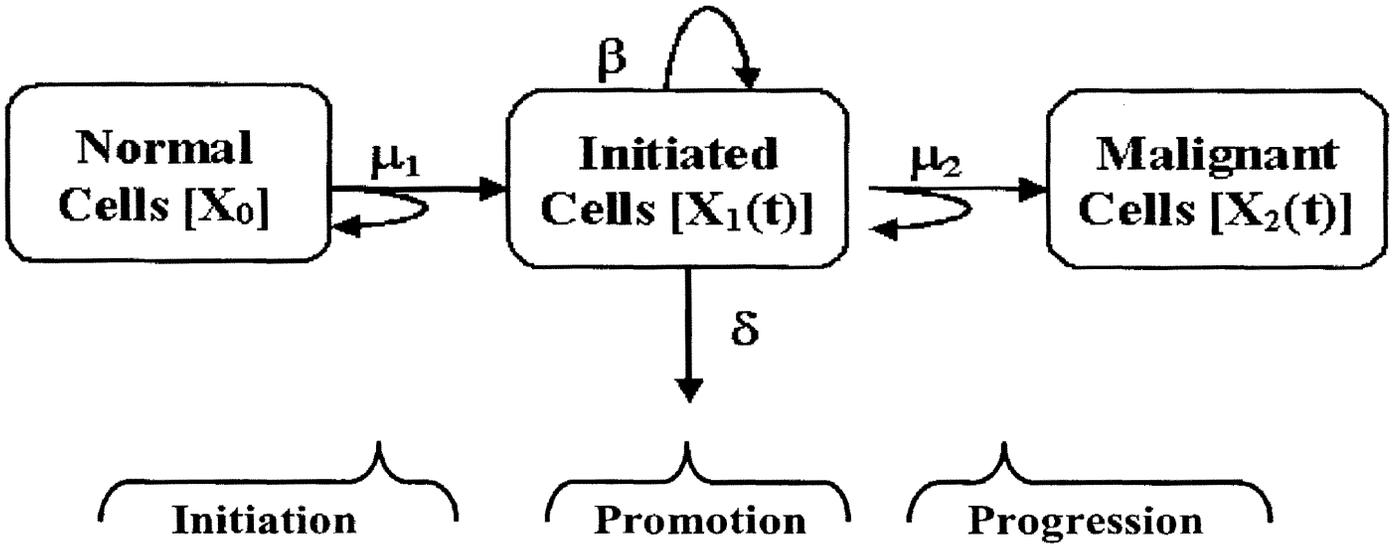

Figure 1 - The two-stage clonal expansion model where μ_1 is the mutation rate of normal cells (per unit time); μ_2 is the mutation rate of initiated cells (per unit time per cell); $\beta$is the birth or replication rate of initiated cells (per unit time per cell); and δ is the death or differentiation rate (per unit time per cell).

The model consists of four time-independent parameters μ_1, μ_2, β, δ seen in Figure 1. Each normal cell has a non-zero probability of undergoing a transformation into an initiated cell at a constant mutation rate of μ_1 per unit time. Where the mutation rate is calculated as the product of the transition rate per unit time per cell and the number

of normal cells, so that $\mu 1=\nu X_0$. Any agent that enhances the probability of such an event is referred to as an initiator. Through replication, initiated cells can develop into clones of initiated cells at a rate of β per unit time per cell, differentiate or die at a rate of δ per unit time per cell, or they can be transform into a malignant cell at a transition rate of μ_2 per unit time per cell (Kopp-Schneider et al. 1994). Any agent that results in an increase in the difference between the replication rate (β) and the differentiation rate (δ), the net proliferation rate, is referred to as a promoter (Heidenreich et al. 1997). Once a malignant cell develops, it loses growth control and in a relatively short period of time will become a tumor; therefore, the formation of a single malignant cell is identified with the development of cancer (Heidenreich et al. 1997;Moolgavkar 1986).

The model's parameters (θ) are always positive so a log-linear transformation is applied to each parameter,

$$\log(\theta) = a + b_0 \, \mathrm{D} + b_1 \frac{\mathrm{D}^2}{100}$$

where the total accumulated gamma or neutron dose is represented as D, a is a constant term, and b_0 and b_1 are regression coefficients. Due to the lack of identifiability that has been shown when estimating the four parameters from tumor incidence data (Hanin and Yakovlev 1996;Heidenreich et al. 1997), the parameter space must be reduced. This can be accomplished by fixing a parameter to a set rate, setting the transition rates equal to another ($\nu = \mu_2$) or the replication rate equal to the differentiation rate ($\beta = \delta$), or reparameterizing the parameter space. It has been shown that the parameter estimates a MLE estimate can be generated using a combination of reparameterization and setting the differentiation rate equal to zero ($\delta=0$) so that

$$\psi = \beta^* - \mu_2^*$$
$$\rho = \mu_1^* \mu_2^*$$
$$\eta = \frac{\mu_1^*}{\beta^*}$$

where the "*" is used to denotes the parameters that are conditioned on δ=0. Maximum likelihood estimates (MLE) of the parameters are obtained using the reparameterized conditional likelihood equation as described in the appendix of Paper II and Paper III. More details on this method and a detailed comparison of the conditional and original likelihood are discussed in Nakamura and Hoel (unpublished paper).

4. DATA SETS

4.1 RERF Atomic Bomb Survivorship Data

The extended Life Span Study (LSS) is the follow-up of the cohort of atomic bomb survivors in Hiroshima and Nagasaki. The doses included in this data set are the most recent estimates using the Dosimetry System 1986 (DS86). This study can be broken into parts; in this study we are interested in both the incidence and mortality data sets for solid tumors and leukemia.

The solid tumor incidence data consists of all survivors that were alive as of January 1, 1958 and follows them through December 31, 1987. This data contains 79, 972 people with a total of 1,950,567 person years at risk after survivors were excluded because they were not in either of the cities at the time of the bombings, their vital statistics were not available, they had DS86 doses greater than 4 Gy, or they had cancer prior to January 1, 1958 (Thompson et al. 1994). Tumor cases were determined by

matching this data with the Hiroshima and Nagasaki Tumor Registry where 8613 cases of solid cancer were reported (Hoel and Li 1998).

For the leukemia incidence data the cohort includes all survivors that were alive as of October 1, 1950 and follows them through December 31, 1987, including 86,293 persons contributing 2,554,000 person years at risk, after elimination of survivors in which vital statistics were unattainable (n=45), DS86 doses were unavailable (n=7103), DS86 doses were greater than 4 Gy (n=262), and people with cancer prior to October 1, 1950 (n=38) (Preston et al. 1994). This cohort is matched with the Leukemia Registry where there are a total of 339 reported cases of leukemia (Hoel and Li 1998).

The most recent follow up for the cancer mortality includes data from 1950 through 1990, which includes an additional 10,500 more survivors with recently estimated doses (approximately 550,000 person-years) bringing the number of survivors to 86,572. There are 7827 cancer deaths of which 7578 are solid tumors and 249 are leukemia (Pierce et al. 1996b).

4.2 JANUS Mouse Data

The majority of the Argonne National Laboratory (ANL) studies, including the JANUS program, were designed to study the biological consequences of occupational levels of exposure to radiation on young adult animals (onset of exposure was at approximately 100 days of age). Between 1971 and 1992 the JANUS program at the Biological and Medical Research Division of Argonne National Laboratory compiled a database on the responses of both male and female F_1 hybrid B6CF1 mice (a cross between C57BL/6Janl ad BALB/cJAnl mice) to external whole body irradiation (Carnes and Grahn 1991). The mice were either exposed to fission neutrons (mean energy 0.85

MeV) or ^{60}Co γ-rays over a range of total doses delivered as either a single exposure or protracted exposures. Three basic patterns of exposure were investigated: (1.) single exposures, (2.) 24 once-weekly exposures and (3.) 60 once-weekly exposures. All irradiations were terminated at predetermined total doses, with the dose calculated at the midline of the mouse. The mice were then followed for the rest of their natural lives; at which point pathology and histology reports were used to determine the cause of death (Grahn et al. 1992).

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PAPER ONE

Corrections in the Atomic Bomb Data to Examine Low Dose Risk.

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ABSTRACT:

Cancer incidence and mortality data from the cohort of Japanese atomic bomb survivors has been adjusted for uncertainty that exists in the dose estimates, systematic error in the neutron dose estimates, and a dose-dependent relative biological effectiveness. Once the adjustments were incorporated in the dose estimates the data was analyzed to allow for the possibility of a threshold dose response. The dose response models that were fit to the data were the same models used in the original papers. A threshold term was included in the model with possible threshold values ranging from 0 to 0.35 Sv. These analyses suggest that for the A-bomb solid tumor and leukemia incidence data a threshold term significantly improves the fit to the purely linear or linear quadratic model. The results from the mortality data suggests that the leukemia data agree more with the threshold model than the linear quadratic model although the linear quadratic model is statistically equivalent, while the solid tumor data does not suggest any improvement with a threshold.

INTRODUCTION:

Radiation protection agencies estimate radiation-induced cancer risks based on epidemiological studies of the Hiroshima and Nagasaki A-bomb survivors, medically irradiated patients, and occupational cohorts using the traditional linear no-threshold model. Debates on the scientific basis of the linear hypothesis have appeared in recent literature (Goldman 1996;National Council on Radiation Protection and Measurements 2001). The linear no-threshold assumption has been adopted as a "*pragmatic guideline in the absence of scientific certainty*" because the complexities of cell responses at low doses cannot be resolved with epidemiological studies. Recent observations—such as genomic instability, bystander effect, and adaptive response are complexities that can modify the response at low doses, which if inducible in humans may invalidate some of the arguments that favor the linear no-threshold model (Kellerer and Nekolla 2000).

The Japanese A-bomb survivor Life Span Study (LSS) cohort is the principal dataset used in assessing the cancer risks following exposure to ionizing radiation (United Nations Scientific Committee on the Effects of Atomic Radiation 1994). This population was exposed at high dose rates; therefore, the risk estimates must be extrapolated to derive estimates of cancer risks for the general public and occupational groups who are exposed to relatively low-dose protracted exposures. Models have been developed to extrapolate between high and low doses from both acute exposure and chronic or protracted exposures, and across time (Cardis et al. 2001). The problem is that these models inevitably introduce uncertainty into the estimates and have been the center of debate for many years.

It is generally accepted that high dose, high dose-rate radiation induced cancer data are well described by a linear dose-response, the issue of interest in radiation risk assessment is the shape of the dose-response curve at low-doses. The problem is that non-linearities are almost impossible to observe or rule out at low-doses in epidemiological data (National Council on Radiation Protection and Measurements 2001). This is because the cancer risks at low doses are too small to observe and confounders exist that cannot be controlled for in human populations. There is also the issue of uncertainty and error in the dose estimates and their potential impact on the dose-response curve. Studies have shown that errors in the dose estimates can substantially alter the shape of the dose-response relationship, thereby nullifying any evidence for possible non-linearity in the dose-response (Little and Muirhead 2000). The issue of uncertainty in the Radiation Effects Research Foundation (RERF) data has been investigated (Jablon S. 1971;Pierce et al. 1990;Little and Muirhead 1997,2000). The presence of random errors in the dose estimates is from the uncertainty that is involved with any dose reconstruction and the bias introduced by the uncertainty in the survivors' location results in an overestimation of dose, and in turn, an underestimation of the radiation effect in dose-response analyses (Pierce et al. 1990).

Another issue of concern with the current dose estimates used by RERF is that discrepancies exist between the calculated and the experimental neutron activation measurements. Experimental activation measurements of thermal (slow) and fast neutrons from ^{36}Cl and ^{63}Ni respectively suggest that a readjustment of the neutron doses is needed (Kellerer and Nekolla 1997;Kellerer and Walsh 2001;Straume et al. 1992). These measurements revealed a systematic underestimation of the neutron component in

the dose estimates, especially at smaller doses (survivors beyond 1 km) (Rossi and Zaider 1996;Little and Muirhead 2000). Recent advancements in accelerator mass spectrometry have made it possible to determine the fast neutron fluences in Hiroshima using ^{63}Ni measurements in copper. Preliminary ^{63}Ni measurements have discounted the earlier tentative correction based on slow neutron activation measurements using ^{36}Cl. The unpublished ^{63}Ni activation measurement data are unconfirmed, although the relationship between neutron and gamma doses was discussed by the National Research Council (National Research Council 2001).

The acute effects of neutron exposure are known from radiobiological studies, while their capability to produce late effects such as cancer, are not known from human observation. The most reliable information on the late effects of neutron exposure comes from experimental animal studies, but due to the uncertainty in these results cannot be directly extrapolated to man. Since neutrons are the more effective ionizing radiation, a lower absorbed dose of neutrons than γ-rays is needed to produce the same biological effect, therefore a relative biological effectiveness (RBE) value is used in calculating the cancer risk estimates of neutrons and γ-rays (Edwards 1999). The dose equivalent, measured in Sieverts (Sv), is simply the product of the RBE and the absorbed dose and results in a risk estimate that can be applied equally to the neutrons and γ-rays. The major analyses of the LSS data have assumed a constant weighting factor of 10 or 20 for the neutron RBE, even though radiation biology has shown that the neutron RBE increases with decreasing dose (Rossi and Zaider 1996). The problem is that RBE cannot be extracted with any certainty directly from epidemiological data (Edwards 1999), an attempt to calculate RBE using the A-bomb data resulted in and estimated RBE of

70 (±50) (Zaider 1991). Rossi and Zaider (1996) and Pierce et al. (1996) present methods using parameters extracted from human lymphocyte aberration data to calculate a dose-dependent RBE that can be applied to the A-bomb data.

Analyses of the unadjusted dose estimates have indicated using linear threshold models (as a surrogate for non-linearity) that the addition of a threshold term significantly improved the linear-quadratic model dose response model for leukemias (Hoel and Li 1998). It has since been suggested that this finding is an artifact of the uncertainties that exist in the dose estimates; and if they were accounted for, there would be no evidence for a threshold in the linear-quadratic model (Little 1999).

The purpose of this paper is to reinvestigate the threshold dose response models after simultaneously adjusting for the uncertainty in the dose estimates, the systematic underestimation of the neutron component as a function of distance from the hypocenter, and a dose-dependent RBE. Specifically we will evaluate the models with the original uncorrected dose estimates, doses corrected for both the uncertainty and systematic error in the neutron dose estimates (using the new fast neutron activation measurement) with a fixed (RBE = 10) and a dose-dependent RBE.

MATERIAL AND METHODS:

The Study Population

The data being used in these analyses is the publicly available cancer incidence and mortality data of the RERF's LSS cohort with doses less than 4 Gy. The solid tumor incidence data includes the 79,972 survivors of the cohort who were alive as of January 1, 1958. The solid tumor cases were determined by matching the survivor data with the Hiroshima and Nagasaki Tumor Registry—as of December 31, 1987 a total of 8,613

cases were found (Thompson et al. 1994;Mabuchi et al. 1994). The leukemia incidence data includes 86,293 survivors who were followed from October 1, 1950 through the end of December 1987, matched with the Leukemia Registry for a total of 339 leukemia cases (Preston et al. 1994). The most recent mortality data has an extended follow-up through 1990 and uses death certificate data for cancer mortality—this cohort includes 86,572 survivors with 7,578 cases of cancer, including 249 cases of leukemia (Pierce et al. 1996b).

Statistical Methods

Poisson regression methods similar to those used in the original studies by Preston et al. (1994) and Thompson et al. (1994) are used in the following analyses. This approach divides the data into cells based on city, gender, age-at-exposure, follow-up time, and weighted organ doses. Using Poisson regression models for cancer incidence assumes that the number of cases in each of the cells is a Poisson random variable with the mean and variance equal to the product of the person years at risk (PYR) and the incidence rate. AMFIT (Preston et al. 1991) is used to fit the model to the data, calculating the deviance, as a measure of the goodness of fit. The deviance is distributed approximately χ^2 with degrees of freedom equal to the difference in the number of cells and the number of parameters included in the model. The addition of a threshold term significantly improves the models if the deviance is reduced by a value greater than the critical value of a χ^2 distribution with 1 degree of freedom (3.84 for α=0.05).

The general class of models for the solid tumor incidence, $\lambda(D)$, and the subtypes of solid tumors are of the form

$$\lambda(\mathrm{D}) = \lambda(c,s,a,y)\cdot[1+\mathrm{ERR}\,(\mathrm{D},e,s,a)],$$

where $\lambda(c, s, a, y)$ is the background incidence rate that depends on city (c), sex (s), attained age (a), and year (y). The other term in the model is the excess relative risk (ERR) which is modeled as a function of the true total dose (D), where the total dose is made up of the dose of γ-rays (D_γ) combined with the product of an RBE value and the neutron dose (D_n), age-at exposure (e), sex (s), and attained age (a).

The leukemia incidence models are similar but are modeled using excess absolute risk (EAR) :

$$\lambda(D) = \lambda(c, s, a, y) + \mathrm{EAR}(D, e, s, t),$$

where t is the time since exposure. The models used in these analyses are those used in the original studies for solid tumor incidence by Thompson et al. (1994), leukemia incidence by Preston et al. (1994), and mortality by Pierce et al. (1996).

Dose thresholds are added to a model of $\lambda(D)$ by defining the cancer rate as

$$\lambda(D|d_0) = \lambda(D - d_0) \quad \text{for all} \quad D > d_0$$

$$= \lambda(0) \quad \text{for all} \quad D < d_0,$$

where d_0 is the given threshold dose (Hoel and Li 1998).

The gamma and neutron doses (d_γ and d_n) available in the data are estimated doses because the true doses (D_γ and D_n) are not known. It has been shown that by replacing $\lambda(D)$ with the average $[\lambda(D|d)]$ in fitting the model,

$$avg\left[\lambda(D_\gamma, D_n \mid d_\gamma, d_n)\right] = \lambda(c, s, a, y) \cdot \left[1 + \mathrm{ERR}(D_\gamma, D_n, e, s, a)\right],$$

the parameter estimates are still approximately unbiased. This method is comparable to the methods used by Pierce et al. (1990) and Little and Muirhead (1996, 1997, 2000). In this analysis, the errors in the neutron and gamma dose estimates are accounted for

separately, similar to Little and Muirhead (2000), where the parametric form of the true dose is the probability of a true dose exceeding any value D and is given by the Weibull distribution $\exp(-\theta_1 D^{\theta_2})$. The parameters θ_1 and θ_2 are found for each combination radiation type, so that the resulting distribution matches that of the estimated doses (Pierce et al. 1990;Pierce et al. 1991). The distribution of the estimated dose given the true dose, f(d|D), is assumed to be log-normal with median D and coefficient of variation d, which is approximately equal to the standard deviation of $\log(d)$. A log-normal model with a geometric standard deviation (GSD) of 30% to 40% was suggested based on the nature of the major sources of uncertainty in the dose estimates (Jablon S. 1971). The results in this paper are based on the log-normal 35% error model.

Since the DS86 neutron dose estimates may be systematically underestimated, a tentative correction was used to bring the neutron doses in line with the measurements of activation by the slow neutrons. The work from Straume et al. (1992) and Kellerer and Nekolla (1997) suggests the following relationship:

$$d_n^c = C(r)d_n$$

where d_n^c is the corrected mean neutron dose and C(r) is the correction factor which is a function of the distance (r) from the hypocenter of the bomb, measured in kilometers. Since the RERF data set does not contain data on distances from the hypocenter, they must be inferred from the relationship between dose and distance as given in Table 40 of Kerr et al. (1987) and the mean shielding factors given in Pierce et al (1996a). The relationship between gamma dose and distance is less dependent on the shielding than the neutron dose (Kellerer and Nekolla 1997), and therefore used as the surrogate for distance in the correction factor C(r). We used very similar methods in calculating a

correction factor to bring the neutron doses in line with the fast neutron measurements. This correction is shown as the ratio of the neutron to gamma dose in Figure 1.

The importance of a dose-dependent RBE in analyzing the A-bomb data is another issue that has been debated. Although most studies have applied dose-independent RBE's, radiation biology suggests the need for a dose-dependent RBE (Rossi and Zaider 1996), which can be calculated from human lymphocyte chromosomal aberration data (Edwards et al. 1980). Since the exposures in Hiroshima and Nagasaki were a combination of γ-rays and neutrons, both doses must be used in calculating the neutron RBE. Using the assumptions of Rossi and Zaider (1996) and the equation for an RBE of mixed exposure from Pierce et al. (1996),

$$\mathrm{RBE}(D_\gamma, D_n) = \frac{\alpha_\gamma}{2\beta_\gamma D_n} \cdot \left[-\left(1 + \frac{2\beta_\gamma}{\alpha_\gamma} \cdot D_\gamma\right) + \sqrt{\left(1 + \frac{2\beta_\gamma}{\alpha_\gamma} \cdot D_\gamma\right)^2 + \frac{4\beta_\gamma \alpha_n}{\alpha_\gamma^2} \cdot D_n} \right]$$

where $\alpha_\lambda = 1.57 \times 10^{-2}\, Gy^{-1}$, $\beta_\gamma = 5.00 \times 10^{-2}\, Gy^{-2}$, $\alpha_n = 83.5 \times 10^{-2}\, Gy^{-1}$ and $\beta_n = 0$, we can calculate an approximate dose-dependent RBE for each dose. In the RERF data sets, small neutron doses (less than 0.001 Gy) are set equal to zero. This problem does not affects risk estimates when the typical RBE values of 10 and 20 are used in calculating dose; however, it has been shown that when the RBE is dependent on dose the smaller doses result in larger RBEs and the problem becomes appreciable. To fill in the missing values of neutrons, a combination of the mortality and incidence data was used to determine the average overall relationship between the neutron dose (d_n) and gamma dose (d_γ), before and after the fast (^{63}Ni) and slow (^{36}Cl) neutron activation measurement corrections were made to the neutron dose estimates, shown in Figure 2. This relationship was then used to replace the percentage of the missing values that

corresponds to survivors whose doses were set equal to zero (the cohort also included an essentially unexposed group sample beyond 3 km) (Pierce and Preston 2000).

RESULTS:

Solid Cancer

In Table 1, the RBE values are calculated for the corrected (adjusted for dose uncertainty and error in the neutron doses) and uncorrected doses and given as an average for each dose group. A ratio of the average dose, with a variable RBE to those with a constant RBE of 10, are given to illustrate the effect of the variable RBE on the total weighted dose, where the weighted dose is calculated as $d_\gamma + RBE(d_\gamma,d_n)\cdot d_n$. The effect of a variable RBE is an increase in the estimated doses for doses originally less than one Sv and a decrease in the dose estimates for those greater than 1 Sv. This finding is more dramatic for the low dose groups once the adjustments for uncertainty and error have been incorporated.

Table 1 - Estimated average RBE values and ratio of the variable RBE dose to the fixed RBE (=10) dose for weighted dose groups using the corrected and uncorrected doses

Weighted Dose (Sv)		< 0.10	0.10-0.25	0.25-0.50	0.50-1.0	1.0-1.5	1.5-2.0	> 2.0
Uncorrected	RBE	46.0	27.6	17.4	10.0	6.1	4.6	3.5
	$\frac{Dose_{RBE(Var)}}{Dose_{RBE(10)}}$	1.07	1.07	1.03	1.00	0.97	0.95	0.94
Corrected	RBE	45.2	26.5	16.9	10.1	6.3	4.7	3.7
	$\frac{Dose_{RBE(Var)}}{Dose_{RBE(10)}}$	1.46	1.25	1.12	1.03	0.96	0.94	0.91

In the original analysis of solid cancer incidence by Thompson et al. (1994), the data were adjusted for city, sex, age-at-exposure, and calendar time, with the excess relative risk assumed to be linear in dose and modified by sex and age-at-exposure. The background risk of cancer is modeled parametrically with a log linear function of city,

sex, year of birth, log age, and log age squared. Hoel and Li (1998) observed that the fitted dose response curve underestimates the number of cancers in the zero dose group while overestimating the lowest exposure group (0.01 to 0.1 Sv), as one would expect in the case of low dose non-linearities. These calculations suggest the possibility of non-linearities in the low dose region of the dose response curve; therefore, a dose response curve that incorporates a linear threshold term was fit to the solid incidence data. In Figure 3, the change in deviance score from the linear no threshold model versus the model's threshold dose are plotted. Three types of dose values are considered: the uncorrected original dose, doses corrected for uncertainty and error with a fixed RBE value, and corrected doses with a dose dependent RBE. We observe that with uncorrected doses and fixed corrected doses, a threshold up to 0.1 Sv appears to improve in the models fit, although there is no significant difference between the linear and threshold models. In the case of the variable corrected dose, the threshold provides a significant improvement in the fit of the model at doses between 0.07 Sv and 0.17 Sv.

Models of solid tumor mortality give a different picture. In the paper by Pierce et al. (1996), cancer mortality is modeled using a stratified background and an excess relative risk that is linear in dose and dependent on sex and age-at-exposure. We see that the addition of a threshold term offers no improvement in the fit of the model, but threshold doses up to 0.15 Sv are not statistically worse from the no threshold model, shown in Figure 4, where the change in deviance is plotted for the three different dose estimates as a function of the threshold dose.

Leukemia

Data on leukemia incidence from Preston et al. (1994) was used to examine the dose response curve for total leukemias. At doses less than 0.30 Sv the linear no threshold model based on the doses available in the RERF data, overestimate the risk of leukemia predicted from the corrected doses and threshold models. A threshold term was incorporated into the models as was done with solid tumors. Figure 5 shows the change in the fitted deviance values plotted versus the threshold doses used in the model. In the cases of leukemias, we see an improvement in the fit of the model with the addition of a threshold. The threshold model provides a statistically better description of the data than is seen with the no threshold model for threshold values up to 0.15 Sv with the uncorrected doses and fixed corrected doses and up to 0.2 Sv for the variable corrected doses. The results of adding a threshold for the subtypes leukemia were similar to the results for the uncorrected doses presented in Hoel and Li (1998). ALL and CML were fit with a dose response function linear in dose while AML as was total leukemia were fit with a linear-quadratic function. For CML the threshold model provided a significantly better description of the data than the no-threshold model, while the addition of a threshold for ALL and AML indicated an improvement in fit that was not statistically better than the no-threshold model. The original, uncorrected doses, as well as, the corrected doses have been fit with a linear-quadratic dose function as shown in Figure 6. We see that the effect of the dose corrections indicate a noticeable difference in the risk estimates even in the low dose region of the curve.

The leukemia mortality data comes from the same paper as the solid tumor mortality by Pierce et al. (1996), but the leukemia models are more complicated.

Leukemia mortality is modeled using a parametrically modeled background and an excess additive risk component that is linear-quadratic in dose and modified by sex, age-at-exposure, and time since exposure. The change in the fitted deviance values is plotted against the threshold doses for leukemia mortality in Figure 7. Although we see an improvement in the fit of the model with a threshold, similar to the leukemia incidence models, the improvement is not significant with the leukemia mortality data.

DISCUSSION:

Theses analyses have shown that the A-bomb survivor data for radiation-induced cancers (solid tumors and leukemias) are consistent with a non-linear dose response model. These findings have been seen with the current dosimetry, as well as with the doses that incorporate information about the uncertainty in the dose estimates, a correction for the systematic error in the neutron estimates, and the incorporation of a RBE value that corresponds with current radiobiological knowledge. The estimated threshold levels depend on the dose estimates that are used. For solid tumor incidence, the incorporation of the uncertainty and error corrections indicate a more pronounced improvement in the fit. Furthermore, when the variable RBE was added, the threshold model became significantly better with an optimal threshold value between 0.10 and 0.15 Sv—in the case of leukemia incidence, the results were the opposite. The uncorrected dose resulted in the most significant improvement with a threshold of about 0.1 Sv, the fixed corrected doses was less significant but with approximately the same threshold, and the variable corrected doses resulted the least significant improvement but with a threshold of about 0.17 Sv. The results from Little and Muirhead (2000) which used a fixed RBE of 20 while correcting for uncertainty in the dose estimates and bringing the

neutron estimates in line with the slow neutron activation measurements indicated similar findings to the results in this paper when the RBE is fixed. The solid tumors incidence data suggests an appreciable upward curvature, although not statistically significant, while the leukemia incidence data indicated a reduction in the significance of the curvature. In these analyses with a fixed RBE, the threshold becomes more significant for solid tumor incidence, although it does not reach statistical significance; while the threshold model for the leukemia data remains statistically significant, the significance of the threshold is reduced.

Multiple imputation (Rubin 1987) is a popular statistical method used with missing data or data measured with error, we applied multiple imputation methods to impute the true dose given the nominal dose for the solid tumor incidence data. A lognormal model was used to impute the true dose given the nominal dose, and 50 multiple imputation datasets were performed. The multiple imputation estimates and standard error estimates were very similar to those obtained using the corrected doses. In particular, using multiple imputation, $\bar{\beta}_{dose} = 1.198$ (estimated standard error 0.3721); using the corrected doses, $\beta_{dose} = 1.186$ (estimated standard error 0.3676). Thus, the similarity of the estimates from these two methods suggests that using the corrected doses will produce unbiased estimates.

The cancer mortality data did not indicate an improvement with the addition of a threshold and appears to be inconsistent with the observation of non-linearity in the low dose region of the dose response curve, even with adjustments for the suggested errors in the doses. This could be due to a bias introduced due to urban-rural differences. Pierce and Preston (2000) observed that the distal group (more than 3000 meters from the

hypocenter) has about a 5% higher cancer mortality rate than estimated for the zero dose group from the proximal survivors. Although the bias is small, it can substantially affect the assessment of risk at low doses.

Other studies have been used to assess the effects of low dose radiation in the production of cancers. A study of cancer mortality in a cohort of Canadian Fluoroscopy patients, fractionated exposures to low LET radiation resulted in a decreased lung cancer mortality than would be expected at the same dose from the A-bomb data (Howe 1995), while the risk of breast cancer mortality was not effected by fractionation (Howe and McLaughlin 1996). Experimental animal studies have also provided information regarding the effect of dose rate on the induction of cancers and have resulted in the recommendation of a dose rate effectiveness factor (DREF) between 2 and 10 for low doses of low LET radiation (Committee on the Biological Effects of Ionizing Radiation 1990). If the effectiveness of radiation is reduced when the exposures are protracted, the result could be an effect of non-linearity at low doses.

Occupational studies of radiation workers have also provided information on the issue of linearity at low doses. However, when total doses are low, occupational data do not provide clear evidence of risk because the precision of these studies is limited by the data and with small exposures, there is the possibility of masking the radiation effect with the "healthy worker effect" that is often associated with occupational studies (Cardis et al. 2001). The curvelinear dose response relationship found for leukemia in the A-bomb data indicates no noticeable risk at doses below 0.20 Sv. Most occupational studies with low cumulative doses have also shown no excess risk of leukemia at low doses, although there are some exceptions (National Council on Radiation Protection and Measurements

2001), although studies have shown that excess risks of leukemia in occupational studies are usually associated with dose greater than 0.4 Sv. The problem with these studies, as with most epidemiological studies of radiation exposure is that they suffer limitations, which impact the interpretation of the data and may make the capability of resolving the issue of low dose risk beyond the capability of epidemiological data alone.

The scientific basis for the no threshold model comes from scientific studies of mutagenesis, clastogenic, and chromosomal aberrations. Mutation frequencies have been shown to increase with either linear or linear-quadratic dose response curves, depending on the radiation quality, LET of the radiation, dose rate, and genetic background of the cell. In either case, there is no direct evidence of a threshold; therefore, if cancer formation is directly related to mutation induction the data does not support a threshold in the cancer dose response, but cannot rule out a nonlinear dose response. Chromosomal studies can only lead to predictions of a threshold if DNA repair is error free at low doses, but the existing data cannot support or refute these predictions. Although a linear no threshold model fits cellular data for many biological alterations that may be precursors for cancer, as well as the epidemiological data, it is important to note that they do not provide evidence that low dose non-linearities or threshold are absent in the data. Further, the discovery of issues such as genomic and chromosomal instability, bystander effects, and adaptive response are currently changing the understanding of radiobiology, and must now be examined to see what effects they have at low doses.

CONCLUSION:

The main conclusion that can be made from these analyses is that even after adjustments are made for uncertainty associated with the dose estimates, systematic error

in the neutron estimates and a dose-dependent RBE a threshold like dose response is still consistent with the A-bomb cancer and leukemia incidence data, reinforcing the findings of Hoel and Li (1998) who found similar results using the uncorrected original doses. And although a linear no threshold model fits the data it does not provide evidence against low-dose non-linearities or threshold models. The shape of the dose response low-dose is an important issue in radiation protection that cannot be resolved with statistics and epidemiology; it will require a better understanding of the radiation biology at low doses and the effects on radiation carcinogenesis.

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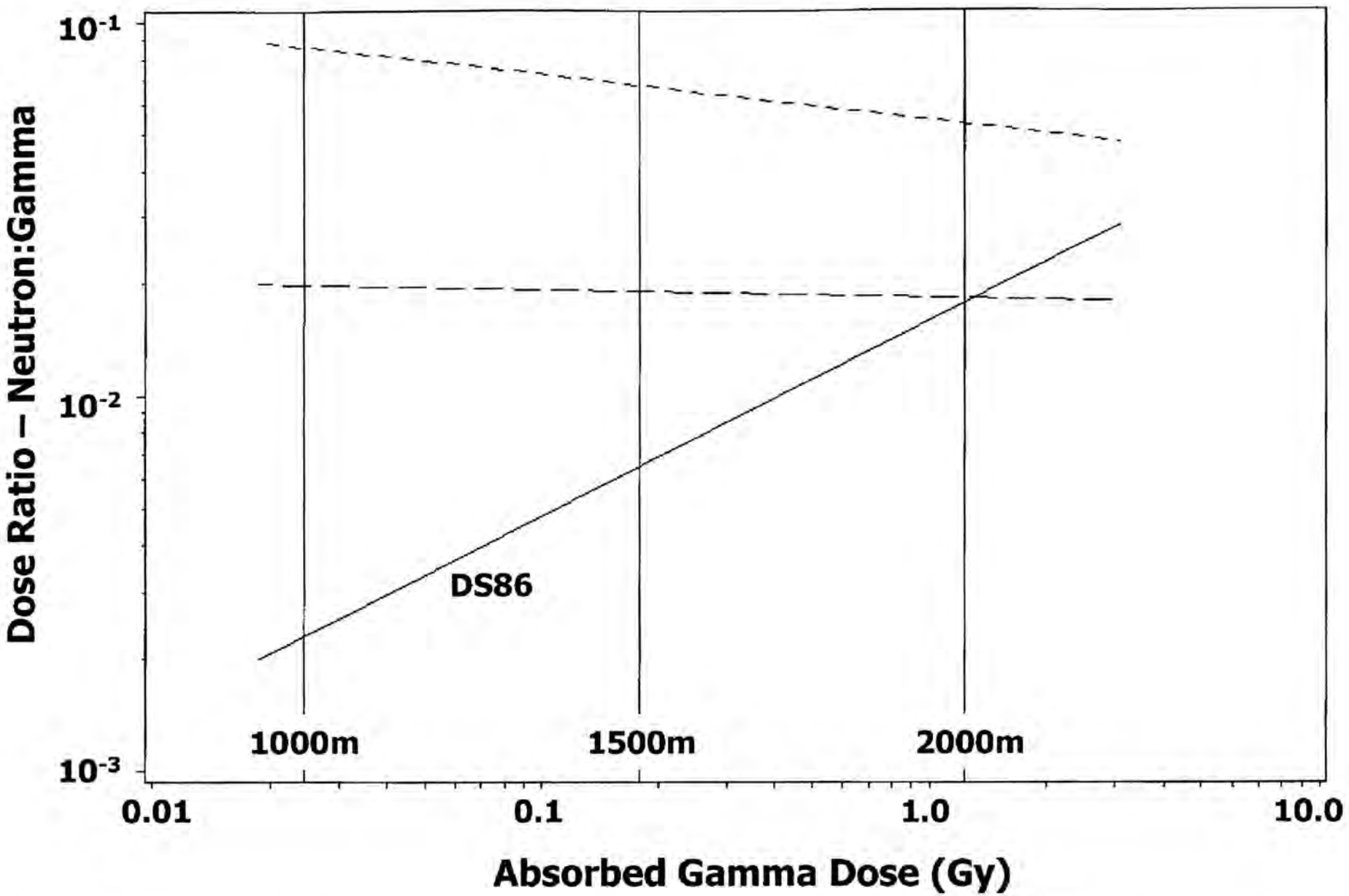

Figure 1 – The ratio of the neutron absorbed dose to the gamma absorbed dose versus the absorbed gamma dose. The doses used are average organ doses, which are equivalent to the marrow doses (Kellerer 2001). The current dosimetry, the DS86 is given as (—); the estimates based on the thermal neutron activation measurements represented by (····) (Straume 1992); (---) represents the estimates based on an intermediate adjustment that is consistent with the available ^{63}Ni measurements from Hiroshima (National Research Council 2001).

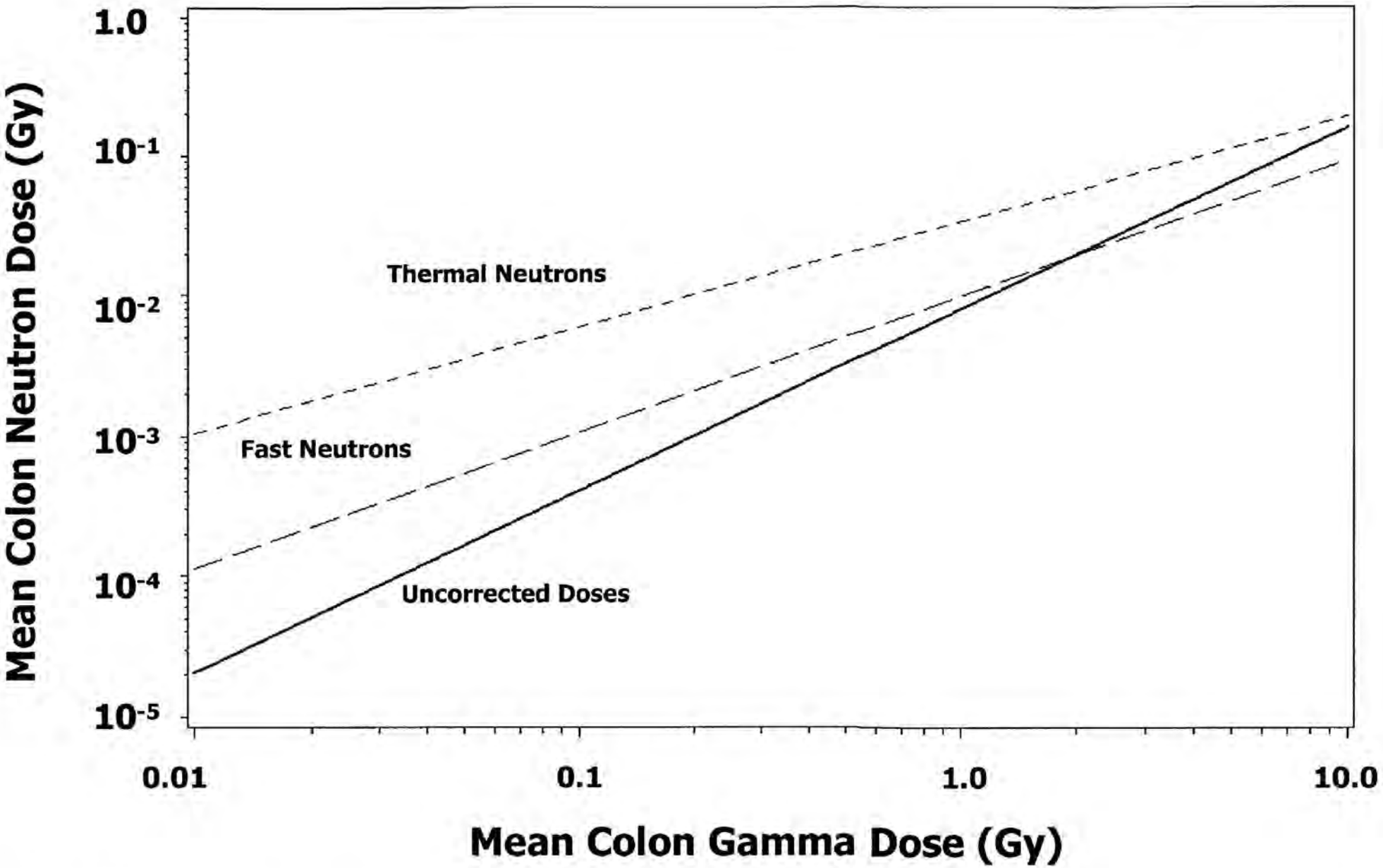

Figure2: The mean neutron doses versus the mean gamma ray doses to the colon in the RERF datasets for cancer mortality and incidence (Hiroshima). The solid line represents the uncorrected doses that are available in the data, the dotted line (---) represents the correction for the slow neutrons combined with the uncertainty correction while the dashed line (— —) represents the fast neutron correction combined with the uncertainty correction of the doses.

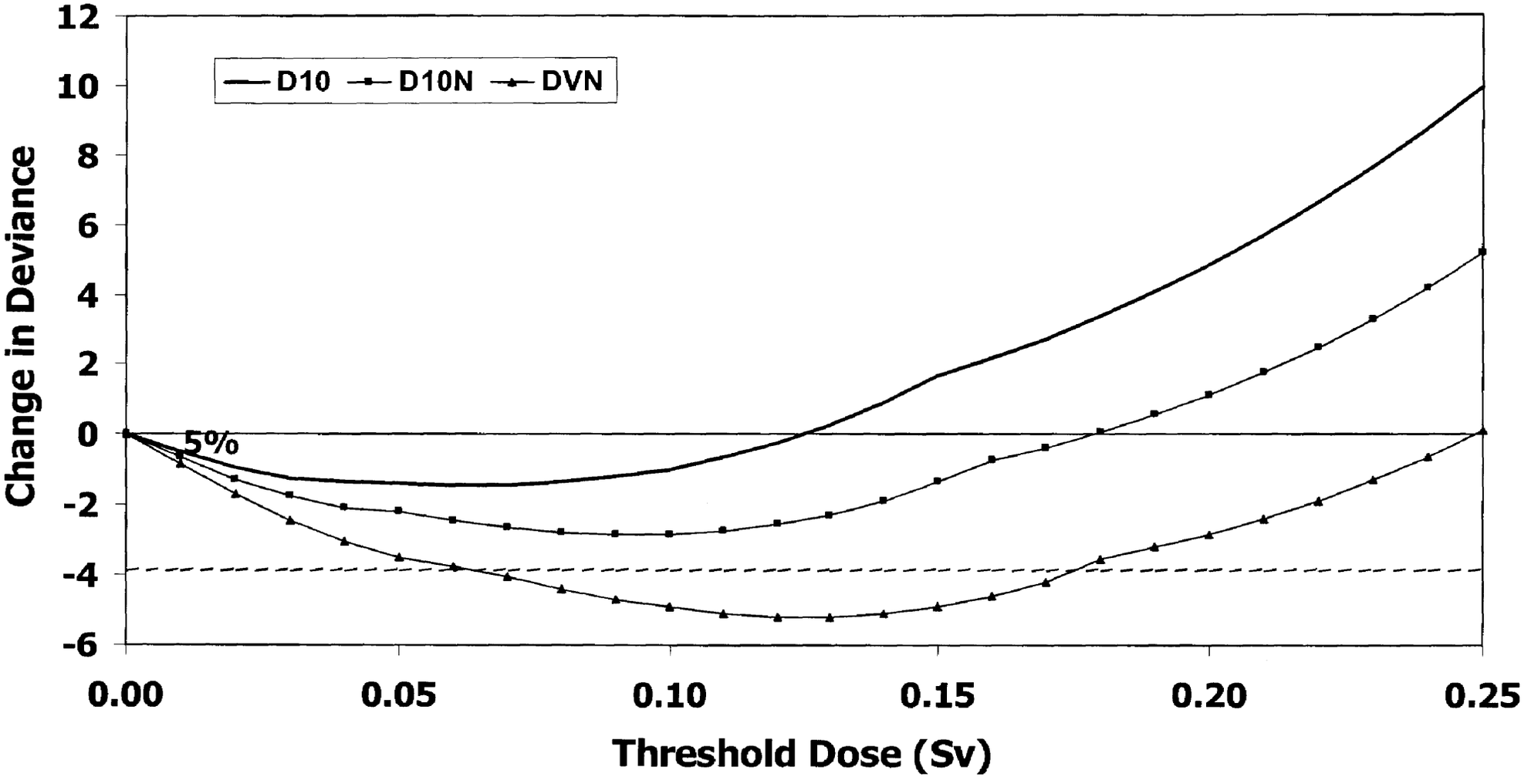

Figure 3 – Plot of the change in statistical deviance from a no threshold model versus the model's threshold value are given for solid tumor incidence. The smaller the deviance value the better the models statistical fit to the data - therefore, the large negative changes in deviance indicate that the threshold model fits the data better than a no threshold model. The horizontal line indicates when the change in deviance is significantly better (p=0.05) than a no threshold model. D10 is the uncorrected colon dose estimates available in the solid tumor incidence data, D10N is the fixed corrected dose estimates, and DVN is the variable corrected dose estimates.

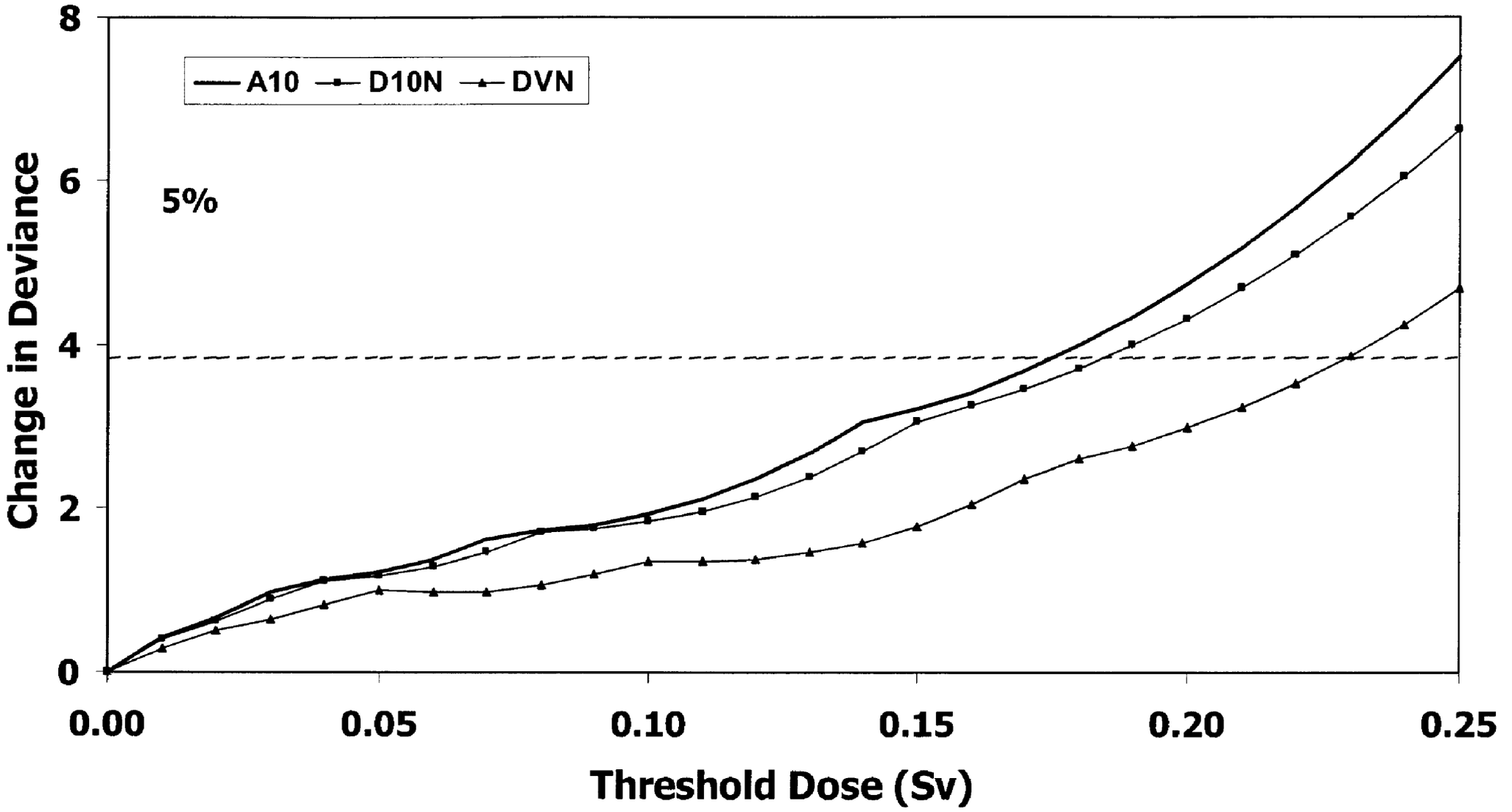

Figure 4 – Plots of the change in deviance versus threshold dose similar to Figure 1 for solid tumor mortality. A10 is the adjusted colon dose with a fixed RBE of 10 that is given in the mortality data, D10N is the fixed corrected dose estimates, and DVN is the variable corrected dose estimates.

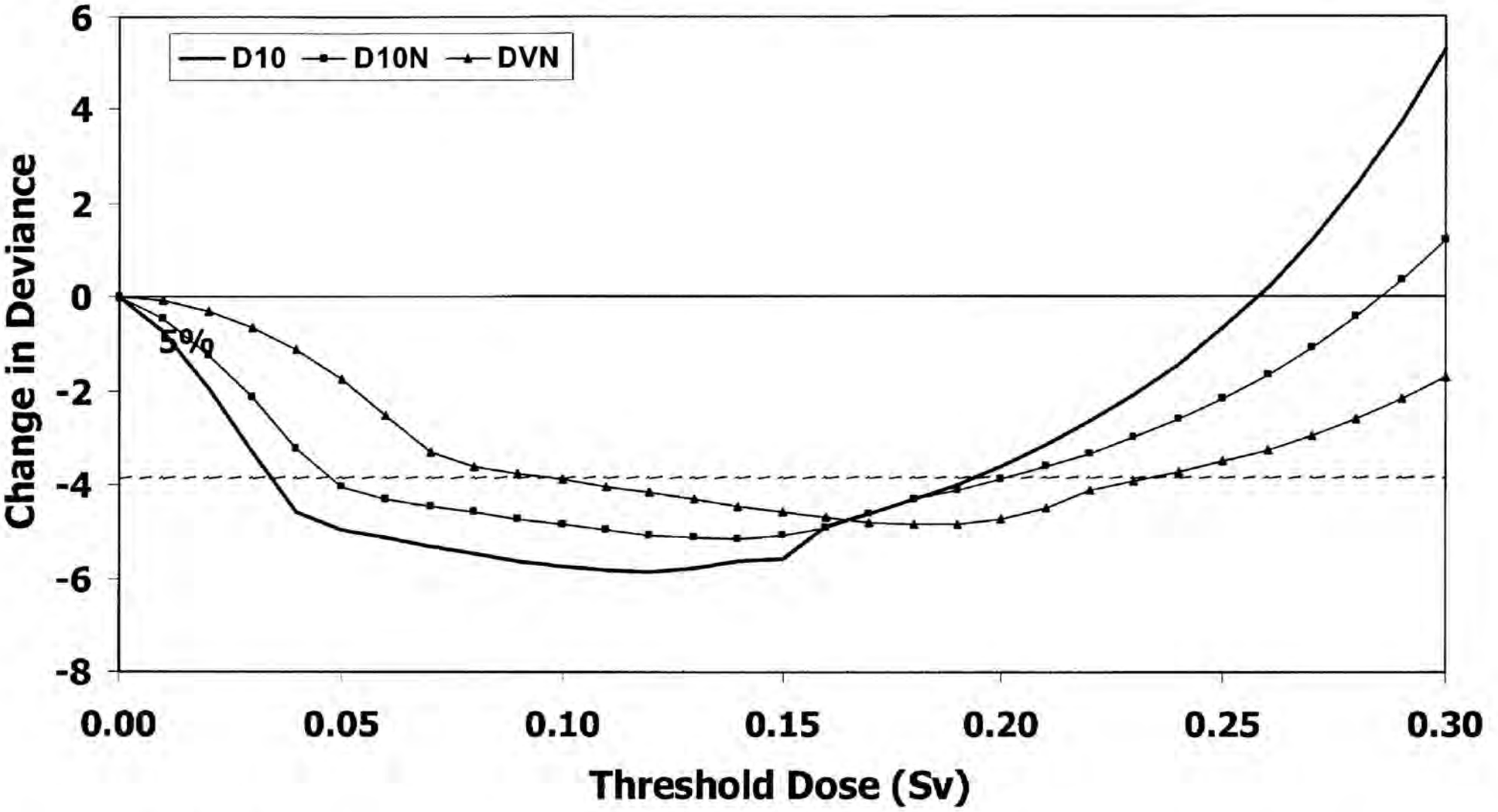

Figure 5 – Plots of the change in deviance versus threshold dose similar to Figure 1 for leukemia incidence data. D10 is the uncorrected marrow dose with a fixed RBE of 10 that is given in the leukemia incidence data, D10N is the fixed corrected dose estimates, and DVN is the variable corrected dose estimates.

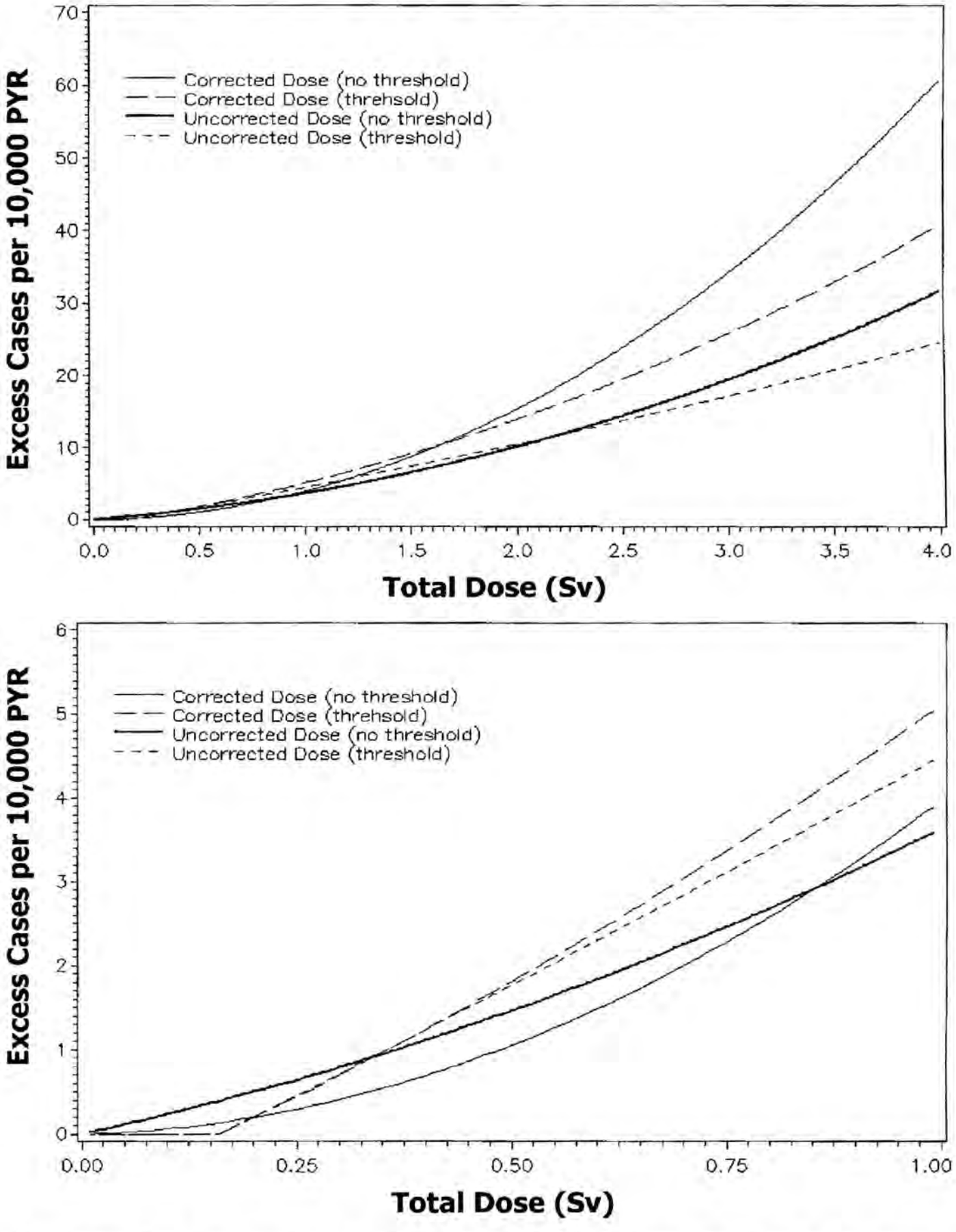

Figure 6 – Dose response curve for leukemia incidence in Hiroshima. Plot of the excess absolute risk of leukemia as a function of dose for males that were 20-39 year old at the time of bombing, 10 years after the exposure. The lower figure depicts the effects of the different models and dose correction at low doses.

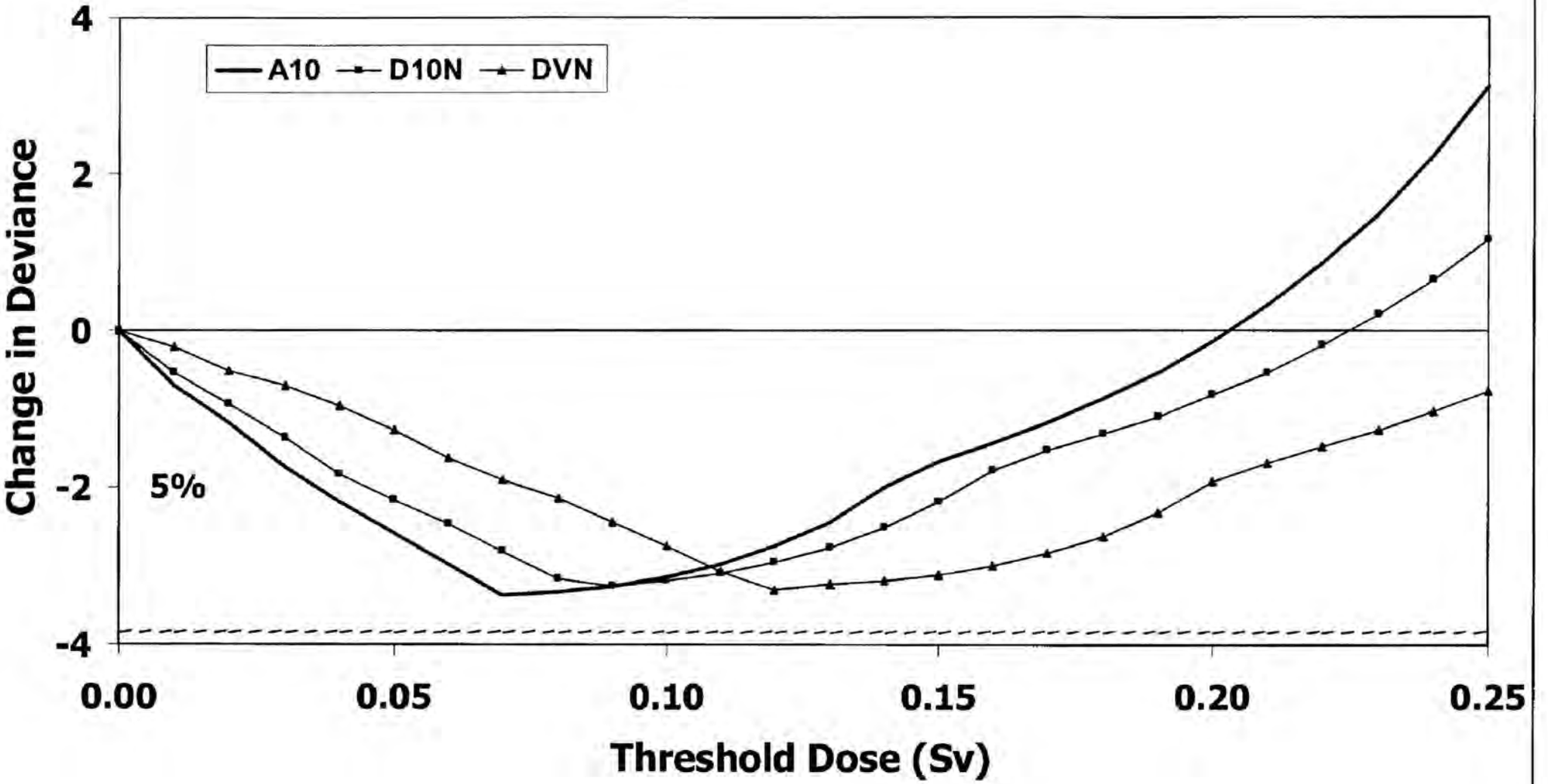

Figure 7 – Plots of the change in deviance versus threshold dose similar to Figure 1 for leukemia mortality. A10 is the adjusted marrow dose with a fixed RBE of 10 that is given in the mortality data, D10N is the fixed corrected dose estimates, and DVN is the variable corrected dose estimates.

PAPER TWO

Comparison of Two Models of Risk Estimation
Part I: Low Dose Region

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Submitted to: Radiation Research

ABSTRACT:

A low dose subset of experimental mortality data from experiments conducted at the Argonne National Laboratory on the effects of exposure of $B6CF_1$ mice to whole-body irradiation, gamma rays (< 300cGy) or fission neutrons (< 30cGy), were analyzed to assess the shape of the dose response and the effects of fractionation. The Cox proportional hazards model was used as an empirical model, while the two-stage clonal expansion model was used as the biologically based cancer model in which information on the carcinogenesis process is incorporated into the model. The two models resulted in similar descriptions of the dose response curves, cancer risks, neutron relative biological effectiveness and dose rate effectiveness factor associated with exposure to ionizing radiation. Both models suggest that a dose-response curve linear in dose provides an adequate fit to the data. Fractionation reduced the effectiveness of gamma radiation while had no noticeable impact on the effectiveness of neutron exposure.

INTRODUCTION:

Many late effects from exposure to ionizing radiation, including cancers, have been described in the literature. The identification and quantification of radiation-induced health effects is an important and complex issue. The recommendations for radiation safety and protection from the International Commission on Radiological Protection (ICRP) are made based on the risk estimates for late effects from low dose radiation (ICRP 1991). A major obstacle in this process is the limited availability of data to directly measure the health effects of radiation on human populations. The problem is further hampered because the data on human exposures do not include the energy spectrum and patterns of exposure that are most relevant. One way to circumvent this problem is to use experimental data from laboratory animals and extrapolate across species to man (Carnes et al. 1998).

Another issue to consider is that there are many models available to generate risk estimates. Some models are empirical, purely mathematical and driven by the data, while others are mechanistic; attempt to incorporate biological plausibility within the mathematics. Both categories of models have a history in radiation biology and different issues that related to them. The Cox proportional hazards model is an empirical model that uses time to event as well as covariate data to describe the data, without considering what is happening biologically. A parametric for of the covariate effect is assumed, while the baseline hazard rate is treat nonparametrically allowing inferences to be made about the covariate effect, but not the baseline hazard. The two-stage clonal expansion model, also referred to as the Moolgavkar-Venzon-Knudson model (MVK model), is a biologically based cancer model that accounts for clonal expansion, replication,

differentiation, and mutation of the cells in the first altered state (initiated cells) as well as the mutation rates of normal cells. Questions as to whether or not non-linearities exists at low doses in the dose-response add to the issue and debate over which model should be used when investigating low dose effects (Hoel and Li 1998).

The two-stage clonal expansion model has been applied to data on radiation-induced cancers in humans and rats as well as other environmental cancers. The A-bomb survivors data indicated an initiation effect, but contained no information on promotion (Kai et al. 1997). In studies of Colorado uranium miners exposed to radon (Luebeck et al. 1999) and radon exposed rats (Heidenreich et al. 2000) a promotion effect was necessary to describe the data.

The two-stage clonal expansion model assumes that at any given time there are a large constant number of somatic cells susceptible to genetic transformation (X_0), since all of the animals in this data were irradiated as young adults, the number of normal cells

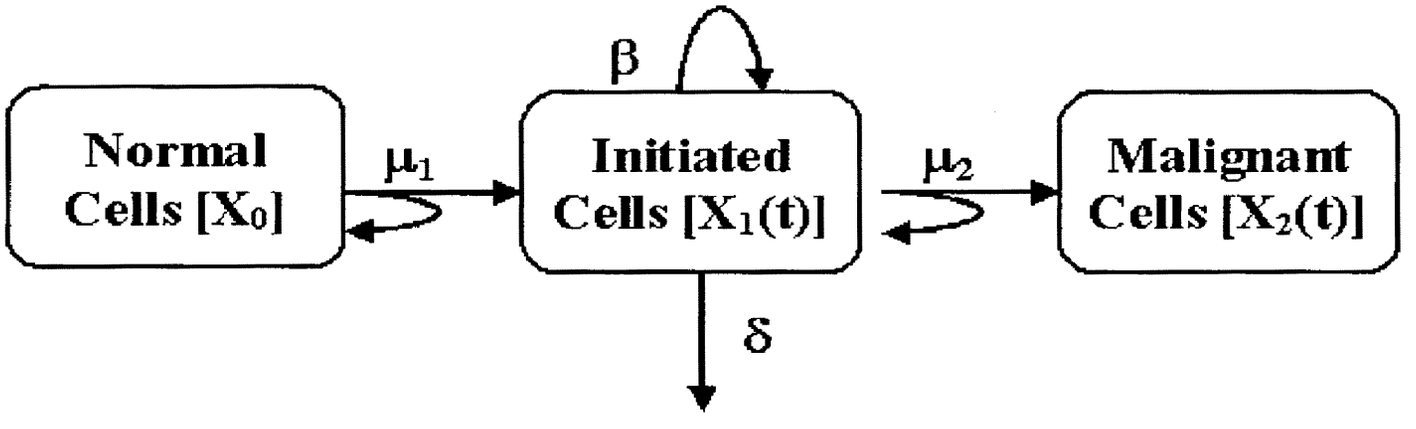

Figure 1: The two-stage clonal expansion model where μ_1 is the mutation rate of normal cells (per unit time); μ_2 is the mutation rate of initiated cells (per unit time per cell); β is the birth / replication rate of initiated cells (per unit time per cell); and δ is the death / differentiation rate of initiated cells (per unit time per cell).

is constant through the observation. Initiated cells, resulting from a somatic mutation ($X_1(t)$) reproduce in a stochastic manner, and once a malignant cell ($X_2(t)$) is formed by a second mutation, it will inevitably become an observable tumor (Moolgavkar 1986; Heidenreich et al. 1997b).

The model consists of four time-independent parameters μ_1, β, δ, and μ_2 described in Figure 1. Each normal cell has a non-zero probability of undergoing a transformation into an initiated cell, at a rate of ν per unit time per cell, so that μ_1 ($= \nu X_0$) is a constant transition rate per unit time. Each initiated cell may undergo three events; they can replicate into two intermediate cells at a rate β per unit time per cell, die at a rate of δ per unit time per cell, or divide into one malignant cell and one initiated cell at a rate of μ_2 per unit time per cell.

There is a lack of identifiability because not all four of these parameters can be determined from tumor incidence data (Hanin and Yakovlev 1996), therefore, it is only possible to calculate three unique estimates for the parameters. In order to solve the system of equations, the parameter space must be reduced either by introducing additional data, reparameterizing the parameter space, or placing a restriction on the existing parameters. In this paper, the parameter space is reduced by reparameterizing into three distinct combinations of the original parameters: (1.) $\psi = \beta - \delta - \mu_2$, (2.) $\rho = \mu_1 \mu_2$, and (3.) $\eta = \frac{\mu_1}{\beta}$ and setting the differentiation rate equal to zero (δ=0).

The two-stage model can be described in terms of initiation, promotion and progression (or transformation). Increasing the probability of a normal cell undergoing a transformation into an initiated cell is referred to as initiation. Promotion is the increase

in the number of initiated cells through clonal growth (increasing the difference between the replication rate (β) and the differentiation rate (δ)). The transformation from an intermediate cell to a malignant cell is referred to as progression. Determining which of the stage or stages in the model are affected by radiation, will in turn, help describes the modifying effect of fractionation.

The objective in this paper is to compare the Cox proportional hazards model with the two-stage clonal expansion model, to see how well they fit the data and what the say about the cancer dose effect of radiation. In doing this we look at what each model estimates for the relative biological effectiveness of neutron, and the dose rate effectiveness factor associated with low dose rates of radiation and how these relate to values used in radiation protection.

MATERIAL AND METHODS:

Data

The JANUS program at the Biological and Medical Research Division of Argonne National Laboratory (ANL) compiled a database between 1970 and 1992 on the response of F_1 hybrid mice, the $B6CF_1$ (a cross between C57BL/6 × BALB/c mice), to external whole body irradiation. Detailed information concerning the individual experiment designs, the animals care and maintenance and radiation factors have been published previously (Grahn et al. 1992,1995).

The data include a total of between 20,000 and 40,000 mice, depending on the level of pathology. The mice were either controls or exposed to ^{60}Co γ rays or fission neutrons (mean energy 0.85 MeV) over a range of predetermined total doses calculated in

centigrays (cGy) at the midline of the mouse. The three basic patterns of exposure investigated were: single exposure, 24 once-weekly exposures, and 60 once-weekly exposures. The average age at onset of exposure was 110 days, in order to study the biological consequences of occupational levels of exposure to radiation on young adult animals. The mice were followed for the duration of their natural lives, at which point pathology judgments based on macroscopic examinations (autopsy) were used to determine the cause of death, as well a subset of these animals were selected at random to undergo a histological examination (microscopic) (Grahn et al. 1992). Comparisons of the macroscopic and microscopic pathology records for primary tumors causing or contributing to death are in agreement 98% of the time (Grahn et al. 1995). This suggests that the macroscopic data, with its larger sample size, can be used reliably for the analysis of these endpoints (Grahn et al. 1992).

For the analyses in this paper, we are only interested in a subset of the JANUS data (Table 1) to examine lowest available doses of gamma and neutron exposures and the effects of fractionating the exposure. Therefore, the data has been restricted to mice receiving total doses less than 300 cGy gamma ray exposures and 30 cGy for neutrons. This restriction resulted in the exclusion of the 24 once-weekly data because of the lack of comparable doses in this dose range. This subset of the data was the basis of the recent analysis reported by Carnes et al. (2002)

Table 1 : Summary of the Mice – Exposure Patterns, Radiation Doses, Sample Sizes, and Mean Ages at Death

Exposure	Dose *	MAD **	Number of Mice	Primary Tumor	
				Cases	Percent
Single Exposure Gamma	0	987	191	149	78
	86	976	189	153	81
	137	947	150	114	76
	198	923	308	262	85
60 Once-Weekly Gamma	0	998	558	483	87
	100	980	562	508	90
	200	967	164	139	85
	300	924	76	68	90
Single Exposure Neutrons	0	981	1026	791	77
	1	988	661	501	76
	2	973	411	314	76
	5	949	312	222	71
	9	932	230	160	70
	19	921	183	148	81
60 Once-Weekly Neutrons	0	997	534	450	84
	2	987	520	429	83
	8	975	204	173	85
	14	924	219	181	83
	22	913	225	193	86

* **Dose** – total accumulated dose measured in centigrey (cGy)
** **MAD (± SE)** – Mean Age at Death given in days

Statistical Methods

On average, the control mice and the mice with lower exposure doses lived longer than the mice exposed to higher irradiation doses (see Table 1). Therefore, for the purpose of comparing the different exposure patterns and dose groups, it is necessary to truncate the populations at a point in time when there are still some mice alive in all of

the exposure groups. For these analyses, the data is truncated at 3 years (1095 days) from the date of first exposure, with any tumors occurring after this date treated as censored.

Dose-response analyses were performed to examine the shape of the dose-response function in the low dose region for each exposure pattern. Primary tumor, defined as all tumors that determined to have caused or contributed to the death of the mouse, is the endpoint of interest in this study. The results were generated using three different models:

(1.) The Cox proportional hazard model (Cox 1972);

$$\lambda(t \mid D) = \lambda_0(t)\exp[\beta' D], \qquad [1]$$

where t, the time variable, is the days at risk, D is a function of the total accumulated dose treated as a continuous variable, $\lambda(t \mid D)$ is the hazard function at time t given dose D for a mouse, $\lambda_0(t)$ is the unspecified baseline hazard function, and $\exp[\beta' D]$ is the relative risk.

To determine the form of dose to be used in the final model three forms of dose were considered.

$$\begin{aligned} &\text{Linear dose} && D = \text{dose}\ , \\ &\text{Linear-Quadratic dose} && D = \begin{bmatrix} \text{dose} \\ \text{dose}^2 \end{bmatrix}\ , \text{and} \qquad [2] \\ &\text{Log-Linear dose} && D = \log(\text{dose})\ . \end{aligned}$$

Each form of dose was modeled for each exposure pattern to determine how well they described the data. The Akaike selection criterion (Akaike 1976) was used to evaluate the least squares fitting to the models and determine which was the most appropriate function of dose to use in the model.

(2.) The piecewise linear Cox model is used to examine the possibility of non-linearity in the low dose region of the dose response curve that would be missed by use of the linear Cox proportional hazards model (Nakamura et al. 1999). This model uses the basic Cox proportional hazards model described above, with the relative risk defined as a linear combination of the original covariate (dose), and a function of the intermediate dose cut points such as the following model for single gamma exposure,

$$\lambda(t \mid D) = \lambda_0(t)\exp[\beta_0 D + \beta_1 D86 + \beta_2 D137] \ . \qquad [3]$$

Table 2 lists the possible dose cut points to be investigated in this analysis for each of the exposure patterns of gamma and neutron. Stepwise Cox regression methods are used to determine which dose cut points, if any, are significant and therefore should be included in the model.

Table 2: Definition of piecewise linear functions.

Single Exposure		**60 Once-Weekly Exposure**	
Gamma	Neutron	Gamma	Neutron
D86 =max{0,D-86}	D1=max{0,D-1}	D100=max{0,D-100}	D2 =max{0,D-2}
D137=max{0,D-137}	D2=max{0,D-2}	D200=max{0,D-200}	D8 =max{0,D-8}
	D5=max{0,D-5}		D14=max{0,D-14}
	D9=max{0,D-9}		

(3.) In the two-stage clonal expansion model, since the parameters (θ) take on only positive values they are modeled in the log-linear form so that

$$\log(\theta) = a + bD \ , \qquad [4]$$

where D is the total accumulated gamma or neutron dose given to the mouse, a is a constant term, and b is the regression coefficient. The maximum likelihood estimates

(MLE) of the parameters are estimated for the conditional likelihood function using a simple transformation of the chain rule. Next, these values are converted into the original parameter values. More details on the method are available in the appendix; and a detailed comparison of the conditional and the original likelihood is dealt with in Nakamura and Hoel (unpublished paper).

To graphically examine and compare the result of the cumulative hazard estimates from the models discussed above, Kaplan-Meier estimates (K-M) of the observed hazard were also calculated for each exposure pattern and dose group as a reference.

RESULTS:

The results of evaluating the possible forms of dose in the Cox proportional hazards model are shown in Table 3. The model was evaluated individually for each exposure pattern; and in all cases, the Akaike information criterion (AIC) was smallest for the linear form of dose, indicating that the linear model was the best fit or was indistinguishable from the other forms of the model. This finding is consistent with previous life shortening studies that found the dose-response curve to be linear for neutrons less than 10-50 cGy (depending on the dose-rate) and for the entire range of gamma irradiation (Storer and Fry 1995;Carnes et al. 1989;Thomson and Grahn 1988;Thomson et al. 1985). Subsequent references to the Cox proportional hazards model will be in reference to the linear form of the model.

Table 3: Akaike Information Criterion Scores for the various forms of dose explored in the Cox proportional hazards model for each exposure pattern.

Radiation Quality	Exposure Pattern	AIC Score *		
		Linear	Linear-Quadratic	Log-Linear
Gamma	Single	**7799.714**	7799.824	7806.817
	Fractionated	**15036.837**	15038.815	15038.152
Neutron	Single	**29724.033**	29725.728	29727.800
	Fractionated	**18426.803**	18428.603	18430.238

* The smallest AIC Score represent the form of the model that best fits the data and is represented in bold face.

The results for our examination of possible non-linearity using the piecewise linear model are given in table 4. For three of the four exposure patterns (all except the fractionated gamma exposure), the selection process for the piece-wise linear model found a threshold dose to be more significant than the simple linear dose. In these cases, the estimated deviance for the threshold model and the linear non-threshold model were used to test whether or not the threshold significantly improved the fit of the model. For all exposure patterns, the results indicate that the piece-wise linear model did not fit the data better than the linear model: single exposure of gamma (p=0.18), neutron (p=0.67), and fractionated neutron exposure (p=0.62).

Table 4 – Comparison of the linear model to that of the piece-wise linear model for each of the exposure patterns.

Radiation Quality	Exposure Pattern	Significant Cut Points *	p-value
Gamma	Single	D137	0.18
	Fractionated	Dose	1.00
Neutron	Single	D1	0.67
	Fractionated	D2	0.62

* Significant cut points are from Table 2

Radiation can affect the initiation rate, promotion rate, progression rate, or a combination of these three rates. Therefore, there are seven different forms of the model that must be considered – those in which only a single stage is affected, those in which two of the stages are affected, and the model in which all three stages are affected by radiation. To determine which of the parameters were affected, we calculated the log likelihood for each of the models. For this data, we determined that the best model to describe all of the exposure patterns is the one in which μ_1 is the only parameter directly affected by dose. Although, for most exposures the other parameters did not behave significantly worse, the μ_1 model was consistently the better model. The slope coefficient of $\log(\mu_1)$ is positive for all exposure patterns (Table 5), indicating an increase in the mutation rate with increasing dose.

Table 5 - Parameter estimates from the two-stage clonal expansion model

Exposure	log(μ_1)		log(β)		log(μ_2)	
	a *	*b*	*a*	*b*	*a*	*b*
Gamma Single	-4.8491	0.001991	-4.8342	--	-12.1220	--
Gamma Fractionated	-4.6357	0.001557	-4.7610	--	-12.6930	--
Neutron Single	-4.5690	0.023354	-4.8943	--	-12.2242	--
Neutron Fractionated	-4.7732	0.023936	-4.7040	--	-12.8462	--

* Each parameter is modeled as $\log(\theta) = a + bD$. (--) value for a parameter indicates that that parameter was not included in the model.

Shown in Figure 2 are the estimated log cumulative hazard rates plotted as a function of time (days at risk), to compare how well the two-stage model (—) and the Cox proportional hazards model (---) fit with the Kaplan-Meier (— step) observed hazard estimates. The two-stage model is a function of time as a continuous variable (see

appendix); therefore, its result is a smooth line, where the Cox proportional hazards model uses individual event times in the model, resulting in a step function. Each figure illustrates the results for the control mice (dose group = 0) as well as a higher dose group; the higher dose groups were chosen to be comparable within each radiation type.

For all exposure groups, both models give a similar fit to the observed values (Kaplan-Meier) after approximately 600 DAR (days since first exposure). Prior to this time, the number of observed events is small and the resulting Kaplan-Meier estimates have large confidence intervals. The difference between the curves for the two dose groups represents the effect of the increase in dose. In Figure 2B, we see that for the same dose there is a noticeably reduced effect for the fractionated gamma exposure compared to the single gamma exposure in Figure 2A. When comparing the neutron exposures (Figures 2C and 2D), there is no visible difference in the effectiveness between the two exposure groups.

The dose-response curves are shown in Figure 3. The Cox proportional hazards (—) and the two-stage clonal expansion model (---) are plotted with the observed Kaplan-Meier hazards and the 95% confidence intervals for each dose group as a reference. The two-stage model estimates the absolute risk for each dose group; consequently, the points of the curve are fixed, while the Cox proportional hazards model results in estimates of relative risk. Therefore, to facilitate comparison, without changing the meaning or estimated risk, the estimated risk of the control group for the Cox model is set equal to that of the two-stage model.

We see, in Figure 3, that the two models predict very similar results for all exposure patterns. Since the dose response curve for all models is linear in the dose

range of this analysis, the main noticeable difference in the two models is the slope of the curves. Once again we can see graphically that the fractionated gamma exposure results in a reduction of the slope of the dose-response curve, indicating a decrease in the effectiveness, while there is no noticeable change in the slope for the neutron exposure.

Dose Rate and RBE

There are two measures that are used in the literature to describe the effects of different radiation quality and dose-rates: relative biological effectiveness (RBE) and dose rate effectiveness factor (DREF). The RBE, as defined in BEIR V, is the biological potency of one radiation as compared with another to produce the same biological endpoint. The DREF is a factor by which the effect caused by a specific dose of radiation changes at low compared to high dose rates (Committee on the Biological Effects of Ionizing Radiation 1990). The DREF used is similar to the dose and dose rate effectiveness factor (DDREF) used by ICRP (ICRP 1991) and UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation 1994) when it is assumed that at low doses the cancer effect is linear in dose.

It is well established in the literature that high-LET radiations have greater biological effectiveness than low-LET radiations (Balcer-Kubiczek et al. 1994;Brenner and Hall 1992). The problem is that the evidence suggests that there is no one RBE value for neutrons, because the RBE value is dependent on the dose, dose-rate, energy, fractionation, target tissue, and time (Carnes and Grahn 1991). The neutron relative biological effectiveness is calculated as the ratio of the linear slope coefficients of the neutron and the reference radiation (ICRU 1986), in this study ^{60}Co gamma.

$$\mathrm{RBE} = \frac{\alpha_n}{\alpha_\gamma} \qquad [5]$$

with $$SE(RBE) = \frac{1}{\alpha_\gamma}\sqrt{\sigma_n^2 + \frac{\alpha_n^2}{\alpha_\gamma^2}\sigma_\gamma^2} \quad ,$$

where σ_γ^2 and σ_n^2 are the variance estimates of the slope coefficients. For single exposure, the RBE estimates are 12.46 (± 4.4) and 11.73(± 4.0) for the Cox proportional hazards model and the two-stage models respectively, while the estimates for fractionated exposures are 19.67 (± 6.2) and 20.69 (± 5.9). The increase in the RBE for fractionated exposures is due mostly (about 80%) to the reduced effectiveness of gamma at the lower dose-rates.

To compare the effectiveness of different dose rates for equal doses, dose rate effectiveness factor (DREF) is used as described above. To estimate the DREF, we fit data obtained at high and low dose rates separately (single and fractionated exposure) and used the estimated slope coefficients to calculate the DREF as

$$DREF = \frac{\alpha_s}{\alpha_f}\left(1 + \frac{\sigma_f^2}{\alpha_f^2}\right) \quad ,$$

with $$SE(DREF)_U = \frac{\alpha_s}{\alpha_f - c} \text{ and } SE(DREF)_L = \frac{\alpha_s}{\alpha_f + c} \quad , \qquad [6]$$

where $$c = \sqrt{\alpha_f^2\left(\frac{\sigma_f^2}{\alpha_f^2} + \frac{\sigma_s^2}{\alpha_s^2}\right)} \quad .$$

The DREF for gamma irradiation is 1.51 (L=1.03 and U=2.45) for the Cox model versus 1.72 for the two-stage model; while for the neutron exposure, the DREFs are 0.94 (L=0.73 and U=1.22) and 0.99 for the Cox model and two-stage model respectively. The values are not different than unity; and therefore, indicate that the dose rate of the neutron exposure at lower doses does not change its effectiveness.

Table 6 presents the relative risk estimates for each exposure pattern and model, with the estimates calculated for total accumulated doses of 100 cGy gamma exposure and 10 cGy neutron exposure. The results indicate that the choice of model does not affect the estimates of risk. Although, they do suggest a reduction in the effectiveness of the gamma exposure with fractionation while the fractionation of neutron exposures indicate no change in effectiveness.

Table 6 - Excess Relative Risk estimates for 100 cGy gamma or 10 cGy neutron radiation exposure for the Cox proportional hazards model and the two-stage model

Radiation	Exposure	Cox Model	Two-Stage Model
Gamma	Single	1.20	1.22
	Fractionated	1.13	1.12
Neutron	Single	1.26	1.26
	Fractionated	1.28	1.27

DISCUSSION:

We performed our analysis on mice exposed to single or fractionated doses of fission neutron or ^{60}Co gamma rays in an arbitrarily selected low dose region (less than 30 cGy neutron and 300 cGy gamma) of the available data, the same subset mice used in Carnes et al. (2002) analysis of non-cancer morbidity. The data for neutron exposure had doses ranging from 0-22 cGy, without any major gaps in the lower doses of the data, which can therefore accurately describe the low dose region, but the data for gamma exposure was much more limited, with the smallest doses being 86 cGy for single exposure and 100 cGy for fractionated exposure. The piecewise linear model and the Kaplan-Meier (K-M) estimates indicate that there may be some form of non-linearity in

the low dose region of the acute gamma exposure. However, the confidence interval of the K-M estimate was large; and without data for doses between 0 and 86 cGy, it is impossible to discern it from a linear model. This unfortunate gap in the data affects our ability to definitively address the issue of linearity in the low dose region of the gamma dose-response curve.

The endpoint of interest in this paper, primary tumors, can be broken down into two subcomponents – lymphoreticular tumors (all leukemia and lymphomas) and solid tumors (all cancer except lymphoreticular tumors). At low doses, all the models for these subcomponents were similar to that for primary tumor for all exposure patterns. The linear Cox model and the μ_1 two-stage model were the best fits; so the only variation was in the slope estimates for the exposure patterns except for single neutron exposure, which indicated no dose dependence for lymphoreticular tumors at low doses.

The RBEs estimated in this analysis are strictly for comparing the two models and are not reliable estimates, because in order to have doses and dose ranges that were comparable between the acute and fractionated exposure, we were forced by gaps in the data to select female mice for the neutron exposure and male mice for the gamma exposure. We see that since the estimated RBEs are based on the slopes estimate and the two models resulted in similar slope estimates, the two models give similar results for RBE (11.73 – 20.69 depending on fractionation). It is interesting to note, that although these estimates are not reliable, they agree well with earlier sex dependent estimates of the RBE for life shortening studies (Thomson and Grahn 1988;Storer and Mitchell 1984). The neutron RBEs resulting from the different studies have ranged from 2 to 100 depending on the dose, dose-rate, cell or tissue type being examined, and cancer endpoint

being examined. The majority of the analyses of the atomic bomb data use an RBE value of either 10 or 20, these being consistent with the quality factor "Q" of 20 recommended by national and international groups on radiation protection (Committee on the Biological Effects of Ionizing Radiation 1990;ICRP 1991).

The reduced effectiveness of gamma radiation seen by both models (DREF = 1.5 and 1.7) has been reported in many studies including previous analyses for the endpoint of life shortening in the JANUS data. Although an increase in the effectiveness of neutron exposure with protracted doses has been reported, it is not seen until higher doses (greater than 40 cGy); and therefore, was not expected to be seen in this analysis (Carnes et al. 1989).

In the two-stage model, the results appear linear for all combinations of dose-dependent parameters in the low dose range investigated. When initiation is the only stage affected by radiation exposure (μ_1 parameter), the dose response curve is linear over all doses with the slope equal to the regression coefficient of the dose term (b) in equation 4. The results of the other models appear linear in the dose range examined, although they are actually non-linear; this non-linearity becomes more evident at higher doses.

It is interesting to note that at low doses, the estimated risk from the two-stage model was not affected by which combination of dose-dependent parameters was used. Therefore, the decision to use the μ_1 model did not have an affect on the resulting risk estimates. In deciding to use the mutation rate model for all exposure groups, we investigated the net proliferation model for the 60 once-weekly neutron exposure because it provided a similar fit to the data, but was much more difficult to interpret in terms of

radiation carcinogenesis. Although the results of the two models are very similar in their risk estimates, their biological interpretations are quite different. It has been generally accepted that most of the biological consequences of ionizing radiation are due to the interaction with the DNA producing changes in the replication and repair (UNSCEAR 2000). These changes are know to take place immediately following exposure and can affect the initiation mechanism. The mechanism of promotion is an increase in the growth imbalance during the time of exposure. This would mean that the radiation would induce a rapid increase in the replication rate (β) or decrease in the differentiation rate (δ), which is not biologically plausible during the brief exposure periods. There are several hypotheses on how radiation could affect promotion, such as negative selection (Mitchel and Trivedi 1992), genomic instability (Little 1998;Wright 1998;Kadhim et al. 2001), and bystander effect (Little and Wakeford 2001) – all of which would explain how a brief exposure could result in lasting effect of the radiation (Little 2000).

From the results presented here, we see that at low doses, the Cox proportional hazards model and the two-stage clonal expansion model (although from completely different theoretical backgrounds and likelihood equations) resulted in similar descriptions of this data and estimated risk. This is because when $\log(\mu_1)$ is the only parameter with a slope coefficient (b), the two-stage model satisfies the proportional hazards model. The difference is in the interpretation of the models and their parameters and baseline hazard estimation process. The Cox proportional hazards model does not specify the baseline hazard function while in the two-stage model the baseline hazard is a function of the constant terms of the parameter estimates, giving biological meaning to the baseline hazard.

CONCLUSION:

The main conclusion that can be drawn from these analyses is that the empirical and biologically based dose response models resulted in very similar descriptions of the low dose data. The two-stage clonal expansion model with μ_1 dependent on dose satisfies the proportional hazards assumptions. Therefore the main difference in the two models is how the background hazard is calculated and the interpretation of the parameters, the empirical values results in a description of the dose effect while the two-stage model allows inferences to be drawn about the background hazards and parameter estimates that relate to the stage of carcinogenesis affected by dose.

ACKNOWLEDGEMENTS:

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APPENDIX:

Two-stage Model Estimation Methods

Let X_0 denote the number of normal susceptible cells in Figure 1. X_0 is assumed large and constant in the study period and $\mu_1=\upsilon X_0$, where υ denotes the first initiation rate per unit time per cell from the normal to intermediate cell. The survivor function S(t), or the probability of no tumor appearance up to time *t*, is given by

$$S(t)=\exp\{-\Lambda(t)\}$$

where

$$\Lambda(t)=\frac{\mu_1}{\beta}\left\{\frac{t(R+\beta-\delta-\mu_2)}{2}+\log\frac{R-(\beta-\delta-\mu_2)+(R+\beta-\delta-\mu_2)e^{-Rt}}{2R}\right\} \quad [A.1]$$

with

$$R^2=(\beta+\delta+\mu_2)^2-4\delta\beta=(\beta-\delta-\mu_2)^2+4\beta\mu_2$$

(Moolgavkar 1986;Kopp-Schneider et al. 1994). The three parameters

$$\psi=\beta\text{-}\delta\text{–}\mu_2\ ,\quad \rho=\mu_1\mu_2 \text{ and } \eta=\frac{\mu_1}{\beta}$$

are identifiable, and the ψ, *a net-proliferation rate*, and ρ, *an overall mutation rate*, are discussed in applications (Moolgavkar et al. 1999;Heidenreich et al. 1997a). However, the complicated form of [A.1] often results in numerical problems in determining the precise MLE of the parameters.

Thus, Leenhouts et al set $\delta=0$ in [A.1] that results in

$$\Lambda(t,\mu_1^*,\beta^*,\mu_2^*,\delta=0)=\frac{\mu_1^*}{\beta^*}\left[\beta^* t+\log\left\{\frac{\mu_2^*+\beta^*\exp\{-(\beta^*+\mu_2^*)t\}}{\beta^*+\mu_2^*}\right\}\right] \quad [A.2]$$

To distinguish between the parameters assuming δ=0 and the original parameters, μ_1^*, β^* and μ_2^* are used in [A.2] (Leenhouts 1999). Leenhouts et al (1999) regard β^* as a net-proliferation rate.

Nakamura and Hoel (unpublished paper) obtain the following exact relationships

$$\psi = \beta^* - \mu_2^*, \quad \rho = \mu_1^* \mu_2^*, \quad \text{and} \quad \eta = \frac{\mu_1^*}{\beta^*} \qquad [A.3]$$

Thus, MLE of the parameters ψ, ρ and η can be obtained from those of μ_1^*, β^* and μ_2^* using the simple transformation. Since μ_2^* is usually much smaller than β^*, $\psi = \beta^*$ should approximately hold.

Briefly, advantage of using [A.2] over the original [A.1] is that appropriate initial trial values may be obtained from two-dimensional grid tables and the iteration searching for the MLE converges even in the method based on [A.1] fails to converge. More detailed comparison between [A.1] and [A.2] is dealt with in Nakamura and Hoel (unpublished paper).

Since the parameters take only positive values, we applied a log-linear model for each parameter,

$$\log(\theta) = a + b\text{Dose} \qquad [A.4]$$

where Dose denotes the exposure doses and a and b denote a constant term and a slope coefficient, respectively. As for the overall mutation rate ρ,

$$\log(\rho) = \log X_0 \nu \mu_2 = a + b\text{Dose}.$$

Since X_0 is constant independent of Dose, we have

$$\log(\nu\mu_2) = a - \log X_0 + b\text{Dose}.$$

That is, the slope coefficient b implies the effect of Dose on the over all mutation rate per

unit time per cell, $\nu\mu_2$, independent of the number of normal cells X_0. The unit time is *day*, and the target tissue is whole body in the radiation data.

The model with only a constant term a for each of the three parameters μ_1, β and μ_2 is referred to as *base model*. The base model is independent of the exposure dose. We obtained the significance of the slope term b for each parameter based on the likelihood ratio test, relative to the base model, in a stepwise manner. It is straightforward that the model with $\log(\mu_1) = a+b\text{Dose}$, but no slope other terms (for $\log(\beta)$ and $\log(\mu_2)$) satisfies the proportional hazards assumption.

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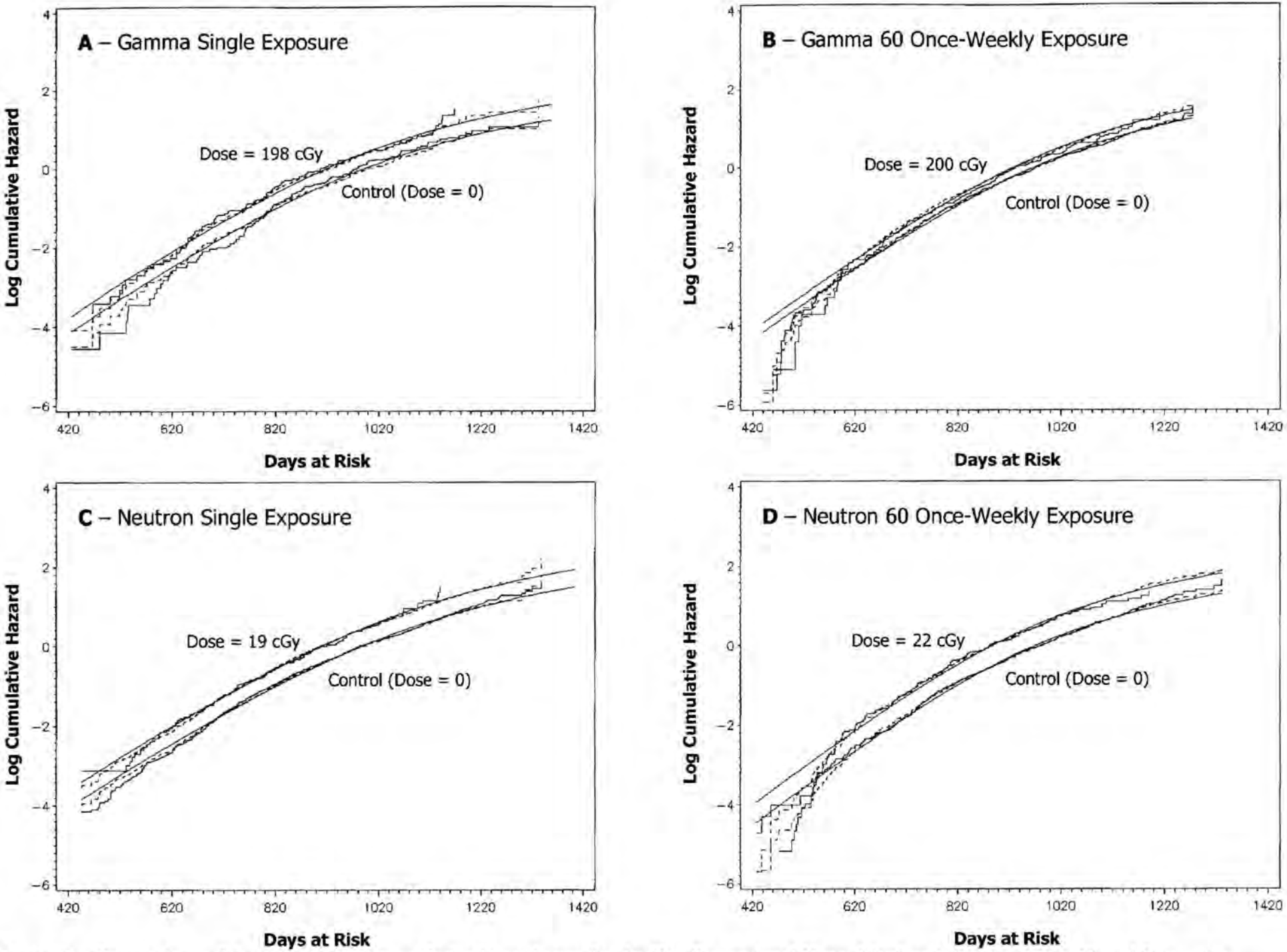
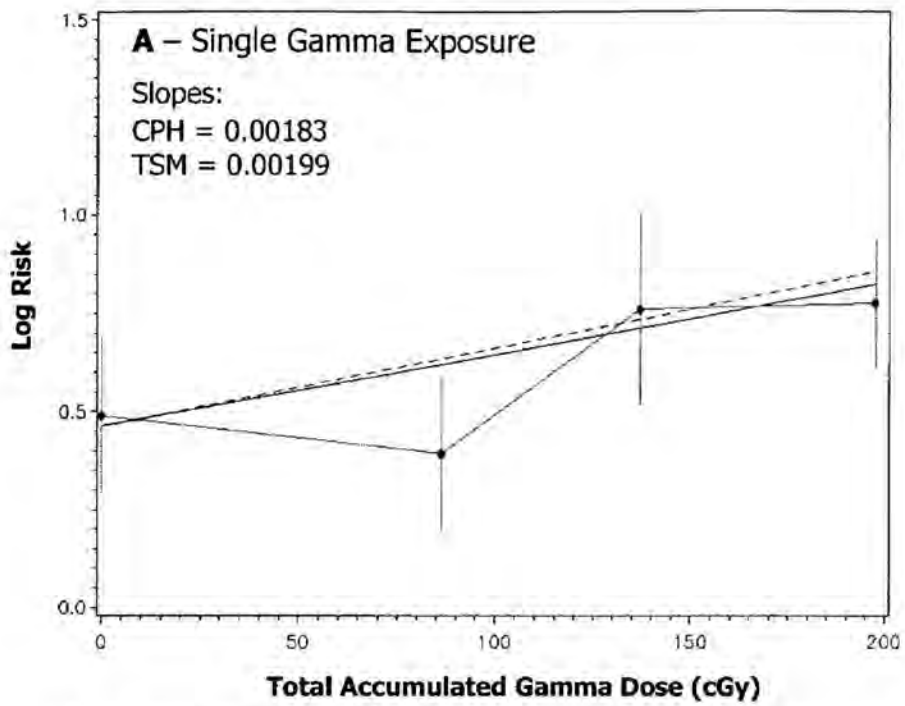
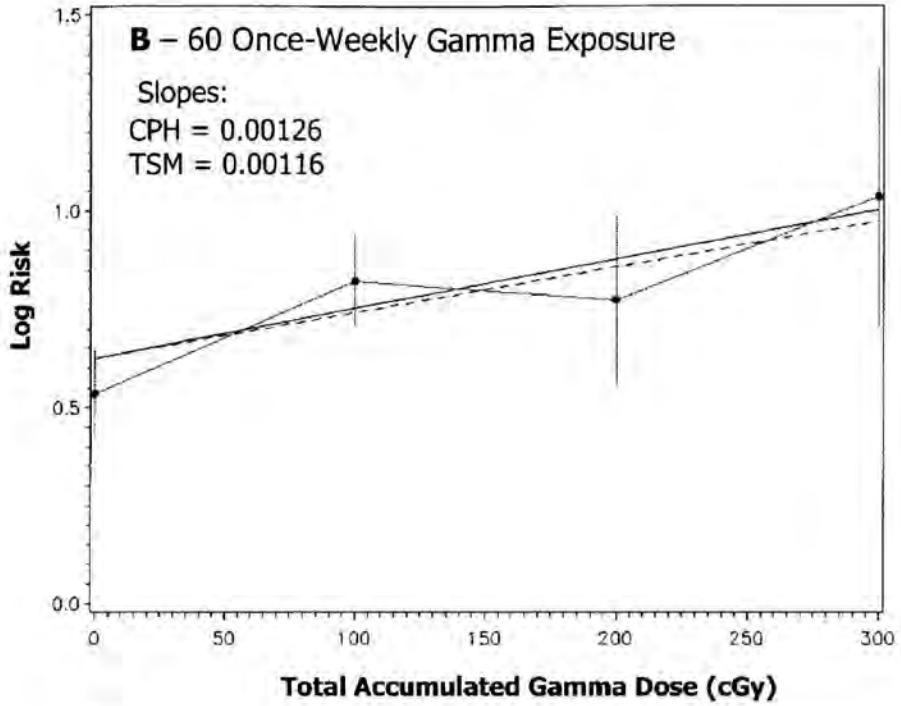
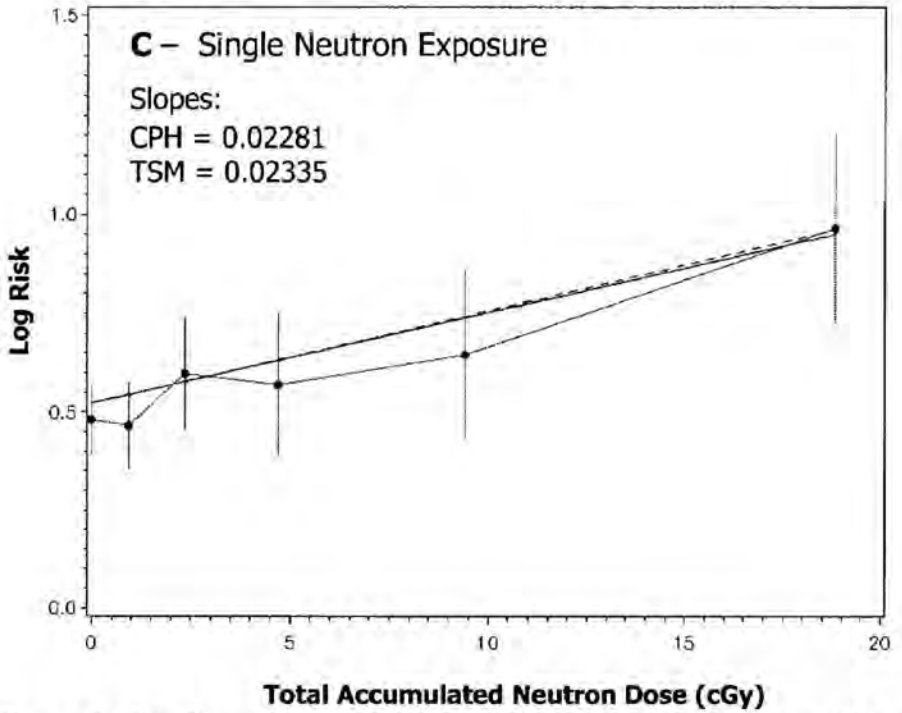


Figure 2 – Comparison of the estimated log cumulative hazard rates for the Cox Proportional Hazard (---) and the Two-Stage Clonal Expansion Model (—) using the Kaplan-Meier observed cumulative hazard rate as a reference (step —). In each graph the three log cumulative hazard rates are plotted for each the control group a higher dose group.







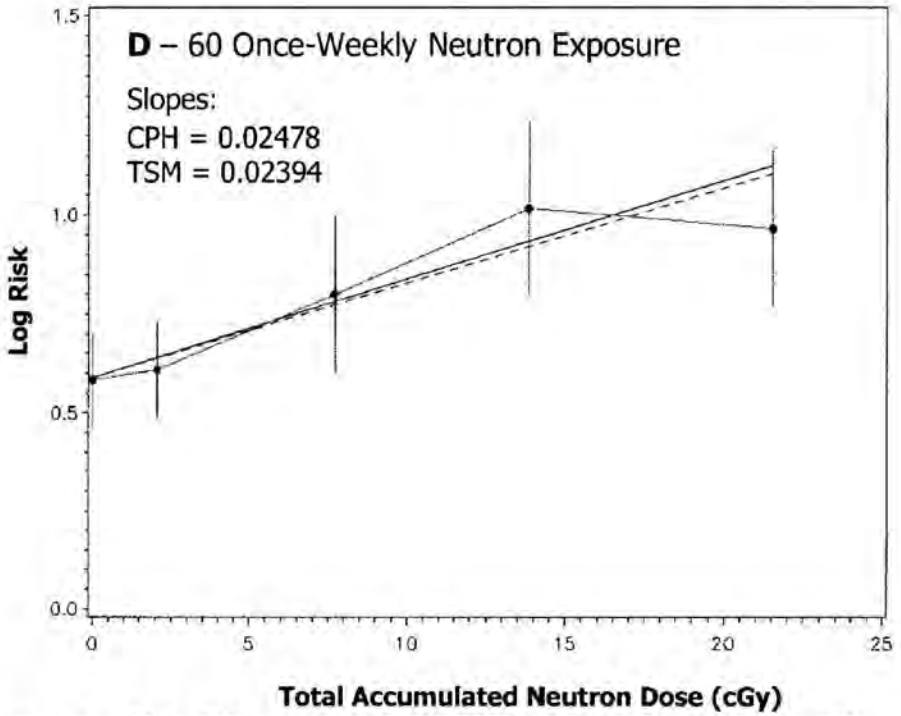


Figure 3: Cox Proportional Hazards (CPH) plots of the relative risk (solid line), Two-Stage Clonal Expansion Model (TSM) plots of the absolute risk (dotted lines), and the Kaplan-Meier plot of the observed risk (dots) for each dose group (with 95% confidence intervals).

PAPER THREE

Comparison of Two Models of Risk Estimation
Part II: Entire Dose Range

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Submitted to: Radiation Research

ABSTRACT:

The analyses in this paper are based on an expanded subset of the experimental mortality data used in Part I. The data comes from experiments using male and female $B6CF_1$ mice, conducted at the Argonne National Laboratory, to study the effects of exposure to whole-body irradiation to assess the shape of the dose response curve and the effects of dose fractionation. The mice were grouped based on their sex, exposure pattern (single exposure or 60 once-weekly exposures) and total accumulated dose of exposure with doses ranging from 0 cGy to 1839 cGy for gamma exposure and 0 cGy to 226 cGy for neutrons. The two-stage model and the Cox proportional hazards model are used to compare the results of an empirical model with a model based on biological information on the carcinogenesis process. Both the neutron and gamma dose response curves appear linear at the lower doses (less than 30-40 cGy), before the nonlinearities become evident. The findings suggest a reduction in the effectiveness of gamma irradiation with fractionation, while the effectiveness of neutrons increases with fractionation.

INTRODUCTION:

The previous paper (Part I) used a subset of the Argonne National Laboratory (ANL) experimental mortality data of $B6CF_1$ mice exposed to external whole body radiation with doses of gamma rays less than 300 cGy and fission neutron less than 30 cGy. In the current analysis, the data set is expanded to include high doses with dose fractionation. The dose response curves are examined for the entire dose range (86 cGy – 1839 cGy gamma and 1 cGy –226 cGy neutron exposure) and the low dose region is compared with the results from the restricted data used in Part I. To enable the comparison of the different models, exposure patterns, and cancer types, the various populations were truncated at a date when mice were still alive in all exposure groups, which in this study included higher doses; therefore, the survival times are censored at 850 days (approximately 28 months) from the date of initial exposure instead of three years as in Part I.

MATERIALS AND METHODS:

The material and methods used in this paper are described in detail in the previous paper. Below is a brief description of the data and statistical methods.

The data used in these analyses is from the database compiled on the response of male and female $B6CF_1$ mice to external whole body gamma, neutron, or sham irradiation from the Biological and Medical Research Division at ANL (Grahn et al. 1995). The same data set (macroscopic data), exposure patterns (single exposure and 60 once-weekly exposure) and diagnosis classification (caused or contributed to death) were investigated. A summary of the number of mice, their mean survival time, and the cases of cancer for each dose group and exposure pattern is given in Table 1.

Table 1 - Summary of the mice included in the analyses: Exposure pattern, Dose (cGy), Number of mice, Mean age at death (± SE), Number of cases of solid tumors and lymphoreticular tumors (percent).

Exposure Pattern	Dose [a]	Number of Mice	MAD [b] (±SE)	Cancer Cases (Percent) ST [c]	LRT [d]
Single Gamma Exposure	0	713	967.76 (± 7)	326 (46)	209 (29)
	86	571	940.95 (± 8)	287 (50)	157 (27)
	137	150	947.18 (±17)	71 (47)	43 (29)
	198	308	923.68 (±11)	150 (49)	112 (36)
	257	179	837.67 (±14)	77 (43)	61 (34)
	400	117	864.03 (±17)	49 (42)	38 (33)
	546	118	758.68 (±21)	34 (29)	40 (34)
	756	184	593.42 (± 9)	31 (17)	60 (33)
60 Once-Weekly Gamma Exposure	0	858	990.01 (± 7)	385 (45)	351 (41)
	100	562	979.45 (± 7)	233 (42)	275 (49)
	200	164	967.52 (±13)	67 (41)	72 (44)
	300	76	924.26 (±21)	30 (40)	38 (50)
	450	82	906.99 (±20)	31 (38)	39 (48)
	600	80	908.15 (±20)	33 (41)	40 (50)
	1839	139	757.01 (±12)	52 (37)	50 (36)
Single Neutron Exposure	0	1725	971.39 (± 5)	499 (29)	741 (43)
	1	661	987.82 (± 8)	181 (28)	320 (48)
	2	411	973.04 (± 9)	124 (30)	190 (46)
	5	312	949.01 (±12)	102 (33)	120 (39)
	9	230	931.75 (±13)	83 (36)	77 (34)
	19	780	892.80 (± 7)	296 (38)	276 (35)
	38	142	869.21 (±16)	69 (49)	45 (32)
	75	185	788.67 (±14)	63 (34)	47 (25)
	151	117	759.60 (±17)	53 (45)	28 (24)
	226	187	697.38 (±13)	54 (29)	35 (19)
60 Once-Weekly Neutron Exposure	0	705	991.22 (± 7)	187 (27)	399 (57)
	2	520	986.84 (± 8)	134 (26)	295 (57)
	8	204	975.03 (±11)	58 (28)	115 (56)
	14	219	924.02 (±11)	71 (32)	110 (50)
	22	225	912.86 (±11)	65 (29)	128 (57)
	31	135	905.47 (±14)	45 (33)	64 (47)
	41	76	837.08 (±18)	32 (42)	29 (38)
	151	152	742.46 (± 9)	68 (45)	41 (27)

a- Total accumulated dose measured in cGy
b- Mean age at death (MAD) given in days plus or minus the standard error (± SE)
c- Solid Tumors (ST)
d- Lymphoreticular Tumors (LRT)

Statistical Methods

The investigation consists of the same basic approach to analyze the dose response of three different cancer endpoints and compare the results as were used in Part I. Of interest in these analyses are primary tumor, lymphoreticular tumor, and solid tumor – where primary tumor is the equivalent to "all cancer endpoints" and can be sub-grouped into lymphoreticular ("all leukemia and lymphoma") and solid ("all cancers other than leukemia and lymphoma") tumors.

The Cox proportional hazards (Cox 1972) model was used to investigate the empirical relationship between dose and cancer. Four functions were evaluated for the parametric form of dose to be used in the model; linear dose $(\mathrm{D} = \mathrm{dose})$, quadratic dose $(\mathrm{D} = \mathrm{dose}^2)$, linear-quadratic dose $\left(\mathrm{D} = \begin{bmatrix} \mathrm{dose} \\ \mathrm{dose}^2 \end{bmatrix}\right)$, and log-linear dose $(\mathrm{D} = \log[\mathrm{dose}])$. The two-stage clonal expansion model parameters (θ) were adjusted to allow for a quadratic term before the log-linear transformation is applied to the parameters

$$\log(\theta) = a + b_0 \mathrm{D} + b_1 \frac{\mathrm{D}^2}{100}$$

where D is the total accumulated gamma or neutron dose, a is a constant term, and b_0 and b_1 are regression coefficients (Moolgavkar 1986).

The relative biological effectiveness (RBE) and dose rate effectiveness factor (DREF) are dose weighting factors used to describe the differences in biological effect for radiation qualities and dose rates. They are calculated based on the initial slope estimates, which for the non-linear and computed from the dose response curves (Committee on the Biological Effects of Ionizing Radiation NRC 1990).

RESULTS:

To determine the function of dose to be used for each cancer type and exposure pattern the Akaike's information criterion (AIC) scores (Akaike 1976) were evaluated for each and are presented in Table 2, with the lowest AIC score marked in boldface. We see that the linear function of dose is the best fitting model for gamma exposure irrespective of the cancer endpoint, while the linear-quadratic fits better for neutron irradiation. The only example where this does not hold true is for lymphoreticular tumors following acute neutron exposure, where the linear model is slightly better, but not significantly different from the linear-quadratic function. Therefore when comparing the results with the two-stage model the linear form is used for gamma exposure and the linear-quadratic form is used for the neutron exposure.

Table 2 - Akaike Information Criterion (AIC) scores for the Cox proportional hazards model for each cancer endpoint examined. The four functional forms of dose evaluated are the Linear (L), Quadratic (Q), Linear-Quadratic (L-Q), and Log-Linear (L-L) functions of dose for each exposure pattern

Radiation Quality	Exposure Pattern	AIC Score [a]			
		L	Q	L-Q	L-L
Primary Tumors					
Gamma	Single	**15028.68**	15035.24	15028.76	15106.02
	Fractionated	**11904.19**	11914.53	11905.35	11971.22
Neutron	Single	29306.62	29367.03	**29268.34**	29279.31
	Fractionated	14122.37	14155.58	**14106.38**	14147.58
Lymphoreticular Tumors					
Gamma	Single	**5992.56**	6001.42	5993.73	6076.81
	Fractionated	**6084.90**	6091.28	6086.12	6121.56
Neutron	Single	**16361.78**	16368.85	16362.97	16369.14
	Fractionated	9184.90	9195.69	**9178.91**	9184.19
Solid Tumors					
Gamma	Single	**9003.20**	9006.17	9005.18	9012.18
	Fractionated	**5821.11**	5825.14	5822.95	5851.47
Neutron	Single	12917.45	12983.81	**12858.12**	12925.62
	Fractionated	4907.53	4932.34	**4893.50**	4927.85

[a] The smallest AIC Score represent the form of the model that best fits the data and is represented in bold face.

Radiation can affect the initiation rate, promotion rate, progression rate, or any combination of these three rates in a linear, quadratic, or linear-quadratic manner. Therefore, there are six different dose related parameters to consider in selecting the optimal model. To determine which of the parameters to include in our model, a stepwise selection procedure was performed in which we found the best model based on the log likelihood at each level of parameters, and then performed likelihood ratio tests to see if the additional parameter significantly improved the fit of the model.

The models that describe the entire dose range are more complicated, and in most cases, requiring more parameters (quadratic terms) to describe the data than was the case when only low doses were considered in the model (Part I). The fractionated gamma exposure the models were an exception, they were best described by a linear promotion model (β is the only dose dependent parameter included in the model). For most of the other exposure patterns and cancer endpoints the model suggests that there are both initiation and promotion effects in the radiation induced carcinogenesis process.

The single exposure patterns all have a positive initiation parameter and a negative promotion parameter, indicating an increasing initiation and decreasing promotion with increasing dose; the models for fractionated exposure patterns have a positive promotion parameter. The neutron exposure models, both the acute and fractionated patterns, have a negative quadratic parameter estimates that causes a downward curve in the dose response at higher doses, similar to a negative quadratic term in the Cox linear-quadratic model.

Table 3 - Parameter Estimates for the two-stage clonal expansion model for each exposure pattern (Exp) and dose range examined.

Exp [a]	Cancer [b]	$\log(\mu_1^*)$			$\log(\beta^*)$			$\log(\mu_2^*)$		
		a^*	b_0	b_1	a	b_0	b_1	a	b_0	b_1
G1	Pr_T	-4.8929	0.00152	0.00043	-4.8137	0.00031	-0.00021	-12.0559	--	--
	Lr_T	-5.2876	--	0.00005	-4.8130	--	-0.00023	-13.0443	--	--
	S_T	-5.6721	0.00280	--	-4.6858	-0.00050	--	-12.0836	--	--
G60	Pr_T	-4.6695	--	--	-4.7387	0.00022	--	-12.7101	--	--
	Lr_T	-5.3706	--	--	-4.7312	0.00023	--	-12.7190	--	--
	S_T	-5.3483	--	--	-4.7485	0.00021	--	-12.6992	--	--
N1	Pr_T	-4.6528	0.04920	-0.0055	-4.8684	-0.00256	--	-12.2134	-0.0251	--
	Lr_T	-5.4542	0.03107	-0.0071	-4.7575	-0.00600	--	-12.3611	--	--
	S_T	-4.9557	0.02547	-0.0082	-4.9682	--	--	-12.5299	--	--
N60	Pr_T	-4.6801	0.00333	--	-4.7372	0.00612	-0.0027	-12.8313	--	--
	Lr_T	-5.2419	--	--	-4.6491	0.00545	-0.0024	-13.0251	--	--
	S_T	-5.4325	0.00585	--	-4.8658	0.00815	-0.0036	-12.7533	--	--

[a] Exposure Patterns (Exp) are Gamma Single (G1), Gamma Fractionated (G60), Neutron Single (N1) and Neutron Fractionated (N60).
[b] Cancer types are Primary tumor (Pr_T), Lymphoreticular tumor (Lr_T) and Solid tumor (S_T)
* Each parameter is modeled as $\log(\theta) = a + b_0 D + b_1(D^2/100)$. (--) value indicates that the parameter was not included in the model.

Plots of the log risk versus total accumulated dose are used to depict the shape of the dose response curve for the each cancer type. In Figure 1, we examine the primary tumor dose-response curve for each exposure pattern. The Cox proportional hazards model (—) estimates the relative risk, while the two-stage model (---) estimates the absolute risk. Therefore, for comparison purposes, without affecting the meaning of the curves, the relative risk curves are adjusted to the absolute risk for the control group (dose = 0). The Kaplan-Meier observed risk (•) and the 95% confidence interval are plotted for each dose group as a reference. Figures 2 and 3 are similar plots for the cancer endpoints lymphoreticular tumors (Figure 2) and solid tumors (Figure 3).

The neutron dose response curves (Figures C and D) indicate that at doses between 40 and 50 cGy, the neutron dose response curve starts to bend downward the effect of the negative quadratic term in the models, as described above. The dose effect of a single exposure to neutrons is less noticeable for lymphoreticular tumor (Figure 2C), the slope is not as steep and only the two-stage model indicates a bend, but not until higher doses (80 to 90 cGy); the Cox proportional hazard model is linear. When the doses were restricted to the low dose range (<30 cGy), the dose effect for lymphoreticular tumors following an acute neutron exposure was not statistically significant (p=0.24). The dose response curve is shown in Figure 4.

In Figure 5 the low dose region of the primary tumor dose response curves from this paper (entire dose range) are plotted against the estimates from the low doses (gamma <300 cGy and neutron <30 cGy) in Part I. The results for the entire dose range are given in red, while the low dose range are denoted in blue. Although they look similar, their interpretations can be different. In comparing gamma single to gamma 60

once-weekly exposures (Figures 5A and 5B) both dose ranges indicate a reduction in the effectiveness due to fractionation, but for neutron exposure (Figures 5C and 5D) the entire dose range and low dose range result in disparate descriptions on effects of fractionation. There is an indication of an increased effect of fractionation when the entire dose range is included in the analysis, while there is no noticeable affect of fractionation when the analysis is restricted to the lower doses.

The RBE estimates and standard errors (Table 5) for these analyses, as in Part I, are for the purposes of comparing the Cox proportional hazard and two-stage models, because they are not adjusted for gender. The two models indicate similar patterns in the RBE values, with values ranging from 1.41 to 23.77 for acute exposures and 24.98 to 46.35 in the case of fractionated exposures. This increase in the RBE values with fractionated exposures is largely due to the reduced effectiveness of gamma with increased fractionation. These values are consistent with values obtained from previous studies, which have ranged from 2 to 100 depending on dose, dose-rate, energy, cell or tissue culture, and cancer type. As seen in previous studies life shortening studies the RBE for lymphoreticular tumors are generally lower than some subtypes of solid tumors and the values for acute exposure are less than fractionated exposures due to the change in effectiveness with fractionation (Carnes et al. 1989).

Table 4 - Estimates of the neutron relative biological effectiveness (RBE) and standard error for primary, lymphoreticular, and solid tumors for each model and exposure pattern

Model	Exposure Pattern	Primary Tumor		Lymphoreticular		Solid Tumor	
		RBE	SE	RBE	SE	RBE	SE
CPH	Single	8.52	1.02	1.49	0.25	22.46	4.66
	Fractionated	34.15	5.38	24.98	6.22	46.35	10.35
TSM	Single	7.06	0.77	1.41	0.18	23.77	3.90
	Fractionated	33.9	4.01	25.02	5.26	43.95	8.52

The models are the Cox proportional hazards model (CPH), the piece-wise linear Cox model (PWC) and the two-stage model (TSM).

In Table 5, the dose rate effectiveness factors for gamma and neutron irradiation are given for each cancer endpoint investigated. In general, the two-stage model and Cox proportional hazards model give similar results for gamma and neutron DREF for each of the cancer sites. Fractionation reduces the effectiveness of gamma exposure, but increases the effectiveness of neutron exposure similar to the finding from previous studies on life shortening (Carnes et al. 1989), tumor mortality (Grahn et al. 1986), and neoplastic transformations (Hill et al. 1985). When only low doses were used in the analysis (Part I) there was no notable difference between the effectiveness of single and fractionation neutron exposure. The DREF value estimated by the two-stage model for lymphoreticular tumors is larger than the estimate based on the Cox proportional hazards model. This is due to the curvelinear nature of the two-stage model (Figure 2A).

Table 5 -Estimates of the dose rate effectiveness factor (DREF) and the Upper (U) and Lower (L) standard error for primary, lymphoreticular, and solid tumors for each model and radiation quality

Model	Radiation Quality	Primary Tumor		Lymphoreticular		Solid Tumor	
		DREF	(U, L)	DREF	(U, L)	DREF	(U, L)
CPH	Gamma	2.53	(2.27,2.83)	3.65	(3.19,4.15)	1.53	(1.23,1.95)
	Neutron	0.64	(0.54,0.75)	0.22	(0.17,0.30)	0.65	(0.51,0.82)
TSM	Gamma	2.85	(2.59,3.14)	5.76	(5.33,6.22)	1.22	(1.03,1.43)
	Neutron	0.64	(0.55,0.74)	0.29	(0.25,0.35)	0.68	(0.56,0.80)

The models are the Cox proportional hazards model (CPH), the two-stage model (TSM)
(U,L) – are the upper and lower values for one standard error from the estimate.

The risk estimates for primary tumors, lymphoreticular tumors and solid tumors are given in Table 6, as well as the risk estimates for primary tumors from Part I. The most notable discrepancy in the risk estimates is for the risk of lymphoreticular tumors from an acute exposure to gamma irradiation, where the two-stage model estimates a 70 % larger relative risk at 100 cGy (1 Gy) exposure. This is due to the curvilinear nature of the two-stage model dose-response, at 450 cGy the results are approximately reversed and the Cox model estimates a 70% larger relative risk than the two-stage model.

The risk estimates indicate that there is very little risk from highly fractionated gamma exposures, which is agrees with the finding from the Canadian fluoroscopy study for lung cancer mortality (Howe 1995). This is interesting because the majority of the solid tumors in the JANUS data are lung cancers. The relative risk estimates based on the mortality studies of the atomic bomb survivors (Pierce et al. 1996) are risk estimates for an acute exposure to a combination of neutron and gamma irradiation, but at doses of 1 Gy the exposure is predominantly gamma rays. The estimated relative risk by gender for solid tumors was 1.17 (male) and 1.44 (female), these values are comparable to the gamma single exposure in our study (which are male mice).

Table 6 - Relative Risk estimates for 100 cGy gamma and 10 cGy neutron radiation exposure for the Cox proportional hazards model (CPH), two-stage clonal expansion model (TSM) and the piece-wise linear Cox model (PWM) for primary tumors, lymphoreticular tumors and solid tumors

Exposure Pattern	Model	Relative Risk Estimate			
		Primary *(Low Dose)*		Lymphoreticular	Solid
Gamma Single	CPH	1.21	*(1.20)*	1.33	1.12
	TSM	1.26	*(1.22)*	1.57	1.11
	PWM	1.19		1.13	N/A
Gamma Fractionated	CPH	1.08	*(1.13)*	1.08	1.08
	PWM	1.10	*(1.12)*	1.10	1.09
Neutron Single	CPH	1.12	*(1.26)*	1.07	1.27
	TSM	1.19	*(1.26)*	1.07	1.28
	PWM	1.25		N/A	2.01
Neutron Fractionated	CPH	1.29	*(1.28)*	1.21	1.46
	TSM	1.32	*(1.27)*	1.26	1.46

Relative risk estimates for primary tumor are given as the relative risk for all doses with the relative risk estimates from when only low doses are included in the analysis in parentheses

DISCUSSION:

We see that in most cases the Cox proportional hazards model and two-stage clonal expansion model result in similar dose response curves, risk estimates, and weighting factors to describe the effect of radiation qualities and dose rates. But there are advantages of using a biologically based model, like the two-stage model such as – they necessitate a better understanding of the disease process being studied, the parameter estimates have biological interpretations, and they increase the credibility of the risk assessment (Goddard and Krewski 1995).

It has been generally accepted that the majority of the biological consequences associated with ionizing radiation are due to a direct interaction with DNA, altering the replication and repair process. There are many types of radiation induced DNA lesions, but misrepaired double strand breaks are considered the essential lesion in the induction of both chromosomal abnormalities and gene mutations (Ward 1995). Of these chromosomal abnormalities and gene mutations it has been suggested that the

inactivation of a tumor suppressor gene, by loss of heterozygosity, is most likely to be the initiating event in radiation carcinogenesis (Little 2000).

For single exposures to gamma and neutron irradiation we see a positive initiation effect combined with a negative promotion effect. It has been hypothesized that in the presence of a strong initiator, such as radiation, an increase in apoptosis would accompany the increase in initiated cells due to initiation, in order to keep the number of intermediate cells in check (Nakamura and Hoel 2002).

The results for most cancer types and exposure patterns indicate that part of the risk from exposure to radiation is its effect on the net proliferation rate, promotion effect. Although it has been suggested that it would not be biologically plausible for a brief exposure to induce the increased growth imbalance necessary to see a promotion effect, it has been proposed that radiation inactivates or kills cells, which are then replaced by the division of neighboring cells. Since initiated cells have a growth advantage over normal cells they fill the void faster than normal cells (Heidenreich and Hoogenveen 2001).

The brief exposure periods experienced by the animals in the JANUS program are quite different from the extended exposure periods used to define chemical carcinogenesis. Therefore a biological rationalization is needed to explain how radiation can cause a change in the parameter values that is constant throughout the entire study period. Recent studies have indicated that radiation may induce some indirect genetic consequences in cells that themselves do not receive direct nuclear radiation. Currently three areas of research into this phenomenon are: radiation induced genomic instability, bystander effect, and cytoplasmic irradiation. The term genetic instability is used to describe a transformation, characteristic of a mutagenic event, which may occur in the

progeny of an irradiated cell, even after many generations of cell replication. This lead to the hypothesis that radiation induces a transmissible genetic instability that has the effect of enhancing the rate of transformation in the descendents of an irradiated cell (Little 2000;Mothersill and Seymour 1998). Bystander effect implies that persistent, genetic alterations can occur in nonirradiated cells due to damaged signals transmitted by neighboring irradiated cells (Little 2000). Furthermore studies have been demonstrated links between a bystander effect and genomic instability; chromosomal instability has been detected in the progeny of nonirradiated cells (Watson et al. 2000). Cytoplasmic irradiation has been shown to induce a significant increase in the spontaneous mutation frequency, while having little effect on cell survival. These phenomenons could play important roles in the carcinogenic effects at lower doses, where fewer cells are in direct contact with the radiation (Lewis et al. 2001) and would increase the probability that a cell could accumulate the mutational events necessary to give rise to a malignant tumor (Kadhim et al. 2001;Little 1998). These findings indicates that the carcinogenic effects of ionizing radiation is not restricted to the direct interaction with DNA and suggest that radiation could act as a chronic exposure.

There is a noticeable downward curvature at higher doses of the dose response curves for neutron exposure. This type of curvature has been seen in this and other mouse data for life shortening effects (Storer and Fry 1995) as well as in the Atomic bomb survivorship data (Shimizu et al. 1990). Cell killing is the likely explanation of the downward curvature at higher doses. It has been shown that a linear model with an exponential cell killing term can be used to describe a linear-quadratic model, where the negative quadratic term indicates cell killing. Although this cannot be estimated directly

by the Cox proportional hazards model, it provides an adequate fit to the Cox dose response curve (Figure 6). The two-stage model does not include a parameter for cell killing and therefore it is not possible to separate the effects of cell killing from the other effects estimated in the model.

Inferences made about the mechanism of actions of an agent based on these analyses must be taken cautiously. Because although the two-stage model is useful in generating hypotheses about the underlying mechanism of carcinogenesis, it has been shown that tumor incidence data does may not have the power to distinguish between initiating and promoting effects (Portier 1987).

CONCLUSION:

These analyses suggest that the empirical and biologically based models result in similar, linear descriptions of the low dose region of the dose response curve. The difference in the two models is seen for single exposures to gamma irradiation with respect to lymphoreticular tumors in which the two-stage clonal expansion models predicts a steeper initial slope of the dose response curve, and therefore a higher DREF and risk of cancer than the Cox proportional hazards model. The parameterization of the two-stage model suggests both the initiation and promotion effects are involved in radiation induced carcinogenesis.

The dose range used in the analysis affected the RBE and DREF values for both models, but did not have much effect on the estimates of risk. When the entire dose range is analyzed the RBE for acute exposures is slightly lower than for the low dose data while the fractionated exposures results in high RBE values. These values are typical of

the RBE values found in other studies, which have ranged from 2 to 100. The results suggest that neutrons exposure appears to have more effect on solid tumors than gamma irradiation (RBE approximately 3 times higher for solid tumors than for all cancers combined) and a very small effect on lymphoreticular cancers (RBE almost 1.5). The DREF values indicate a reduction in the effectiveness of gamma irradiation with fractionation, while the neutron indicated an increased effectiveness when the entire dose range is analyzed.

The resulting nonlinearities in the dose response curve become evident at higher doses as has been seen in life shortening studies. In particular the dose response curves for the different cancer endpoints following neutron exposure bend downward at higher doses, possibly indicating a cell killing effect. To determine the best approaches to radiation protection, the issue of non-linearity in the dose response curve will have to be settled based on a better understanding of the radiobiology associated with radiation carcinogenesis.

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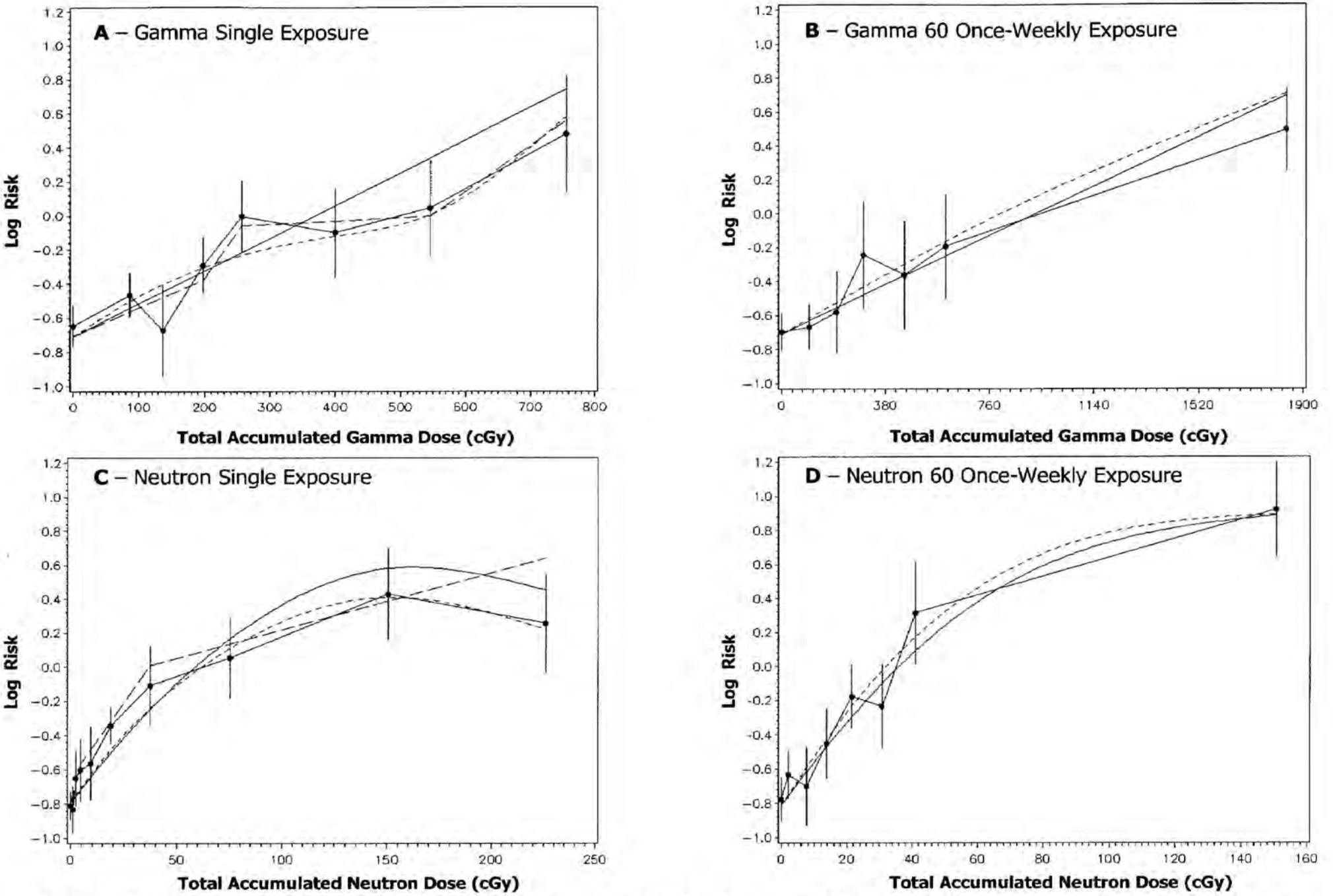

Figure 1 – Plots of log(risk) of primary tumors for each exposure group. Cox Proportional Hazards (CPH) plots of the relative risk (—), Two-Stage Clonal Expansion Model (TSM) plots of the absolute risk (---), Piece-wise Linear Cox Model plots of the relative risk (— —) and the Kaplan-Meier plot of the observed risk (-●-) for each dose group (with 95% confidence intervals).

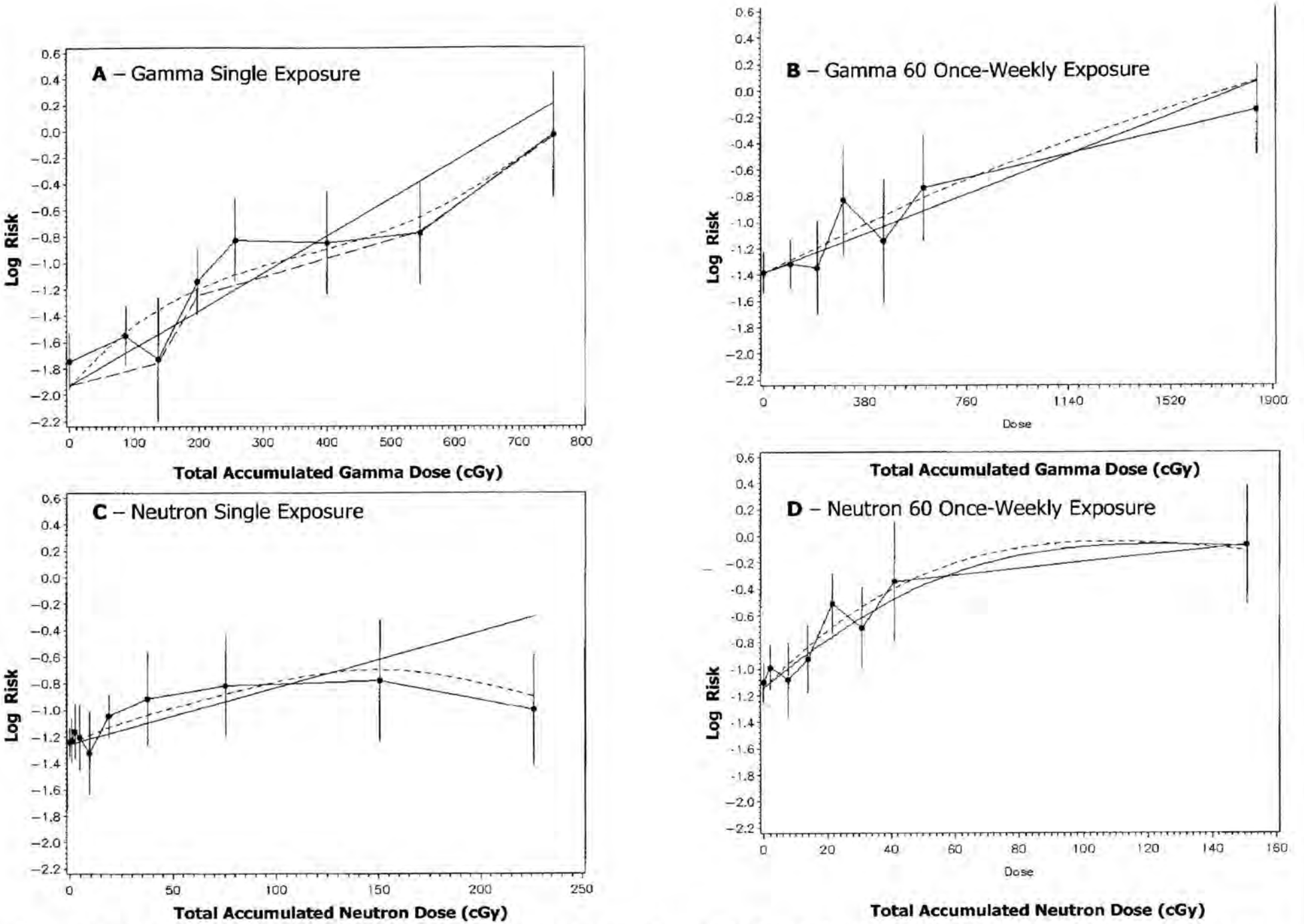

Figure 2 – Plots of log(risk) of lymphoreticular tumors for each exposure group. Cox Proportional Hazards (CPH) plots of the relative risk (—), Two-Stage Clonal Expansion Model (TSM) plots of the absolute risk (---), Piece-wise Linear Cox Model plots of the relative risk (— —) and the Kaplan-Meier plot of the observed risk (-●-) for each dose group (with 95% confidence intervals).

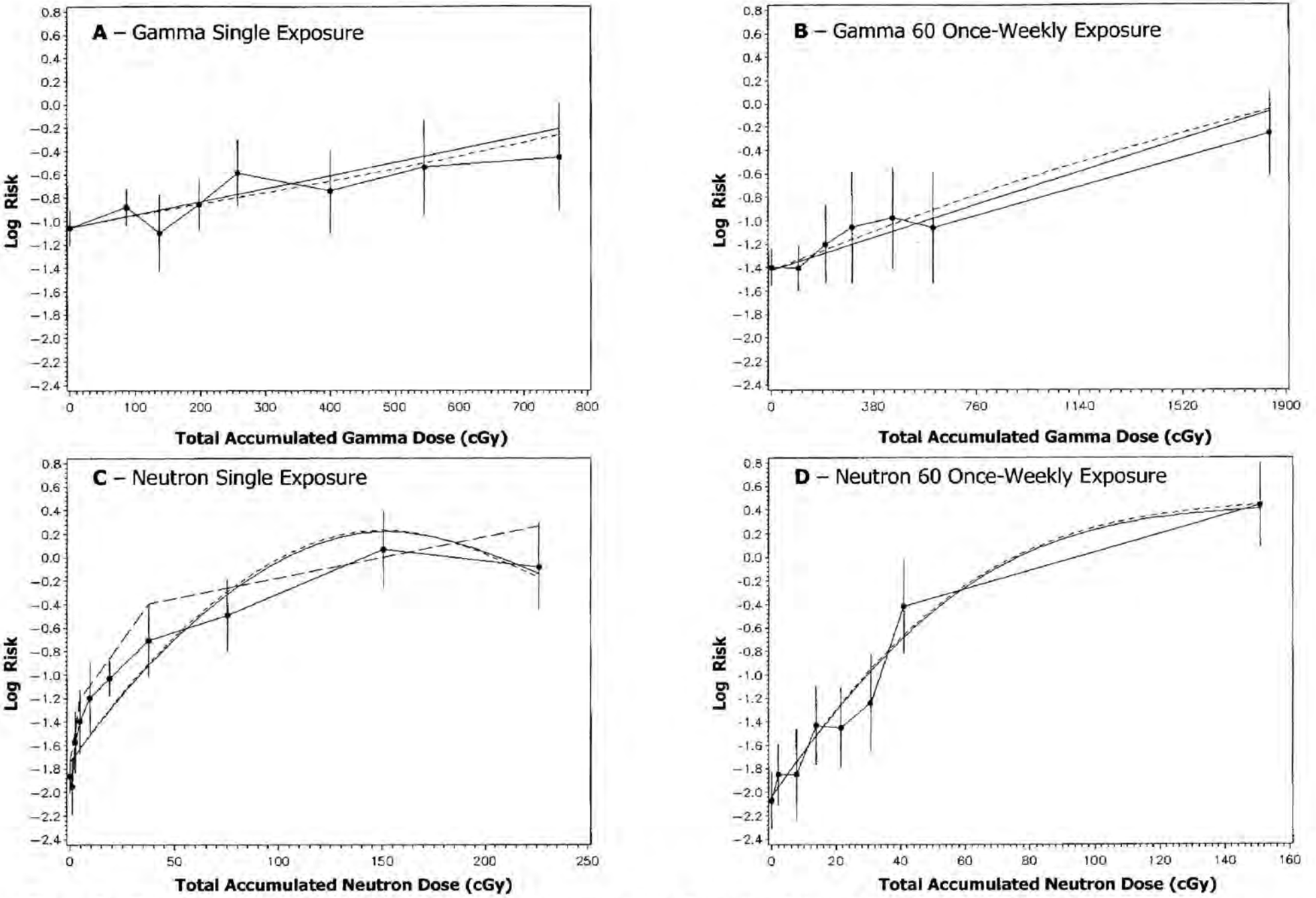

Figure 3 – Plots of log(risk) of solid tumors for each exposure group. Cox Proportional Hazards (CPH) plots of the relative risk (—), Two-Stage Clonal Expansion Model (TSM) plots of the absolute risk (---), Piece-wise Linear Cox Model plots of the relative risk (— —) and the Kaplan-Meier plot of the observed risk (-●-) for each dose group (with 95% confidence intervals).

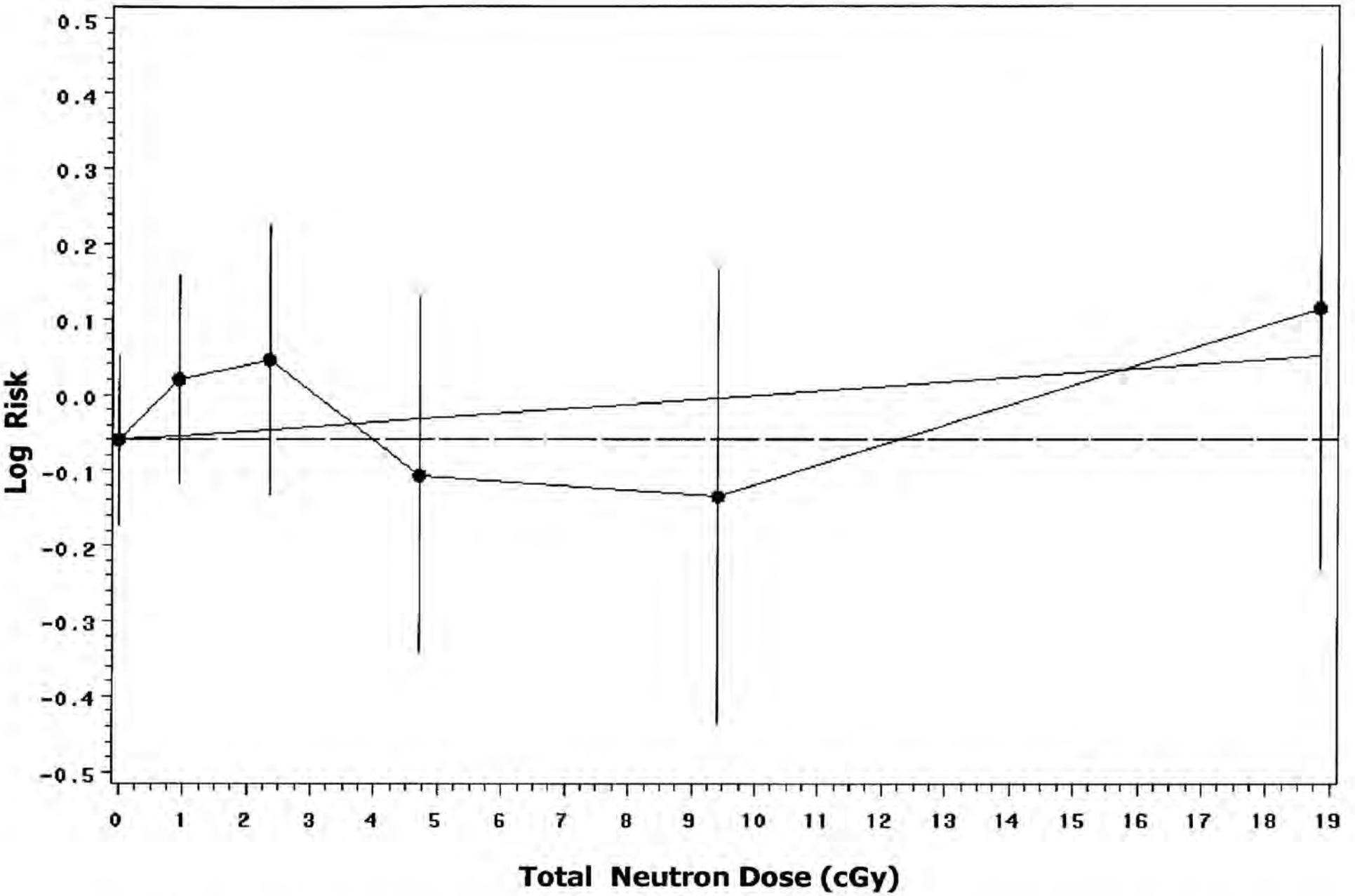

Figure 4 – Plot of log(risk) of primary tumors following a single neutron exposure when the data is restricted to the low dose range (< 30 cGy). Cox Proportional Hazards (CPH) (—), the Kaplan-Meier plot of the observed risk (—●—) for each dose group (with 95% confidence intervals) and a reference line for no effect (---).

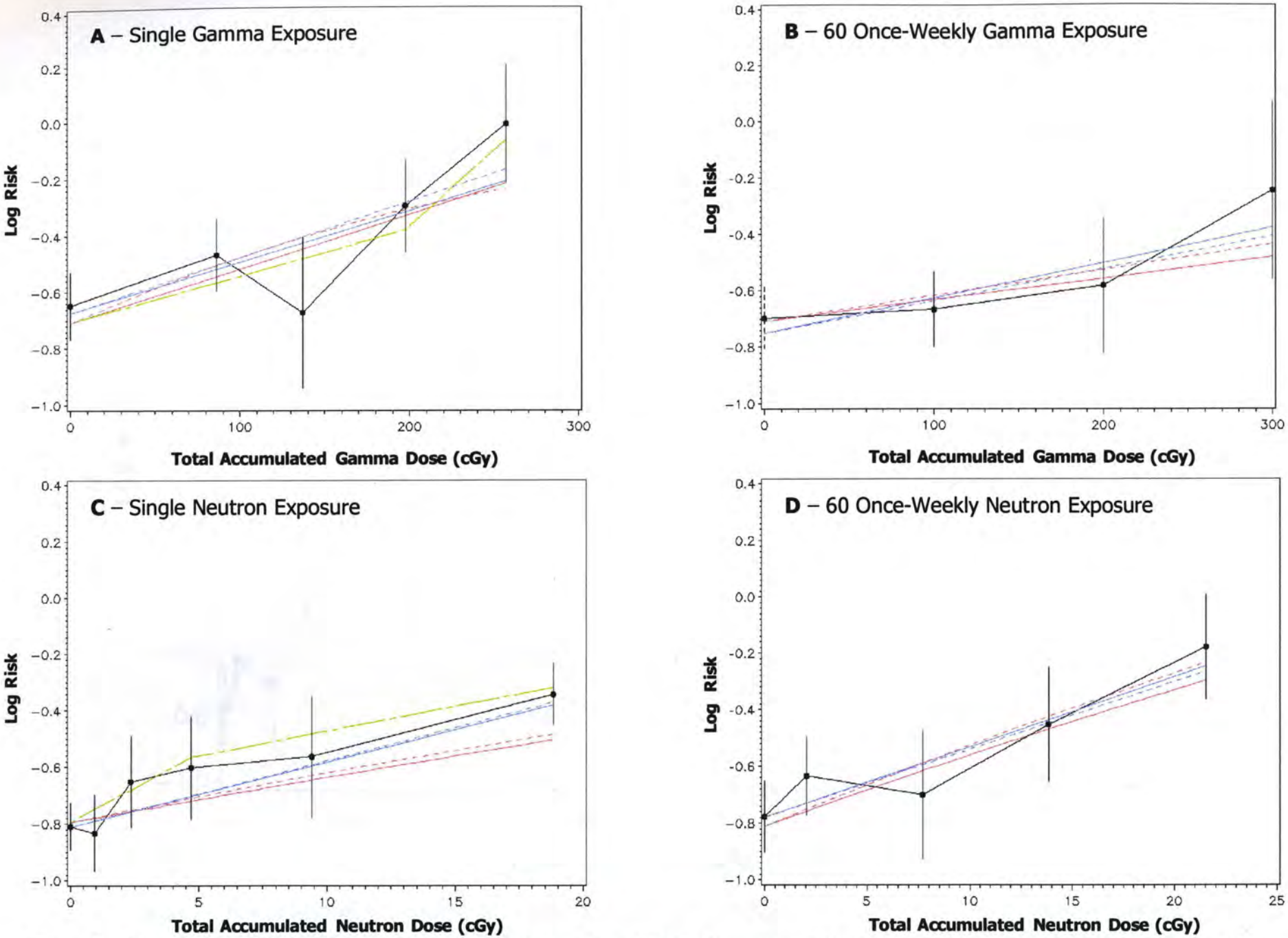

Figure 5 – Plots of log(risk) for each exposure group for the low doses (<300 cGy gamma, <30 cGy neutron) . Cox Proportional Hazards plots of the relative risk for entire dose range (—) restricted to low doses (—), Two-Stage Clonal Expansion Model (TSM) plots of the absolute risk for the entire dose range (---) restricted to low doses (---), Piece-wise Linear Cox Model plots of the relative risk (— —) and the Kaplan-Meier plot of the observed risk (—●—) for each dose group (with 95% confidence intervals).

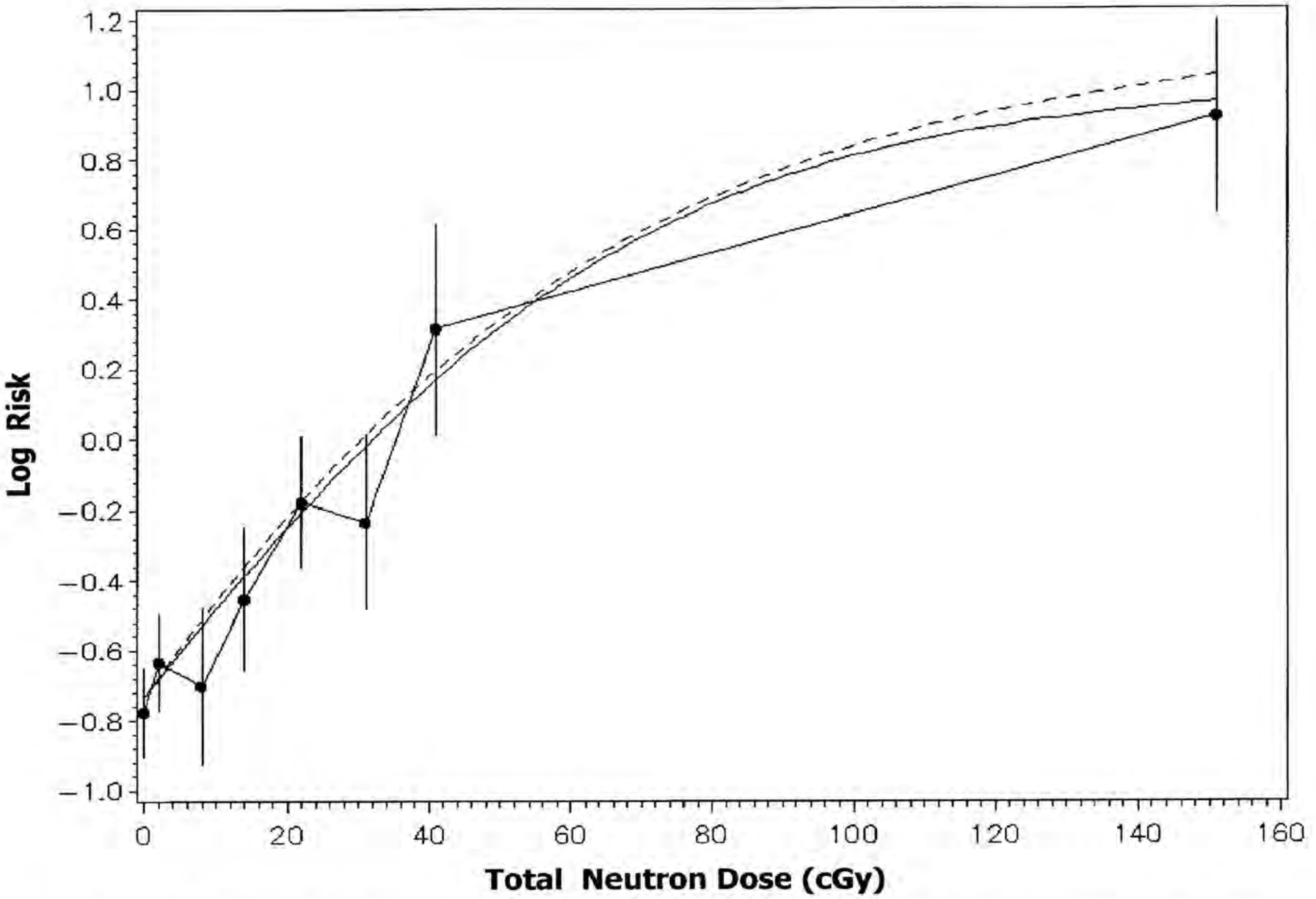

Figure 6 – Plot of log(risk) of primary tumors following exposure to neutrons. Linear quadratic Cox Proportional Hazards (CPH) (—), a linear with cell killing (---) line fit to the Cox estimated dose response curve, and the Kaplan-Meier plot of the observed risk (-●-) for each dose group (with 95% confidence intervals).

7. SUMMARY

The purpose of this research was to evaluate the low dose region of the dose response curve for cancer risks from ionizing radiation. Although this has been examined and reported in the past, errors in the dose estimates have been shown to alter the shape of the dose response curve at low doses. In the analyses of the atomic bomb data the appropriate corrections were made to the dose estimates and the models fit to the corrected dose to see if previous findings indicating non-linearities at low doses were still found or if they were simply an artifact of the errors in the dose.

In Paper I a threshold was included in the model, as a surrogate for non-linearity. The threshold model was found to significantly improve the fit of the solid tumor incidence model when the doses are adjusted for uncertainty and systematic neutron error, and the neutron RBE is considered dose-dependent. The non-linearity that was seen previously in the uncorrected leukemia incidence data was still present after the dose adjustments, therefore providing further support for the use of a non-linear model at low doses. The mortality data did not indicate a significant improvement in the fit of the data although, the threshold and no threshold models were indistinguishable at lower doses. Only the solid tumor incidence data did not indicate an improvement with the addition of a threshold, similar to the results of the uncorrected doses.

Papers II and III look at the ANL mouse data to gain insight into the modifying effect of fractionation on gamma and neutron exposures. In Paper II only the lower doses were included in the analyses, and resulted in a linear models for both radiation qualities, independent of the exposure pattern. The two-stage model was best fit with the μ_1 model in which initiation was the only stage dependent on dose. Both models, the Cox

proportional hazards model and the two-stage clonal expansion model resulted in the same description of the data, with the two-stage model reducing to a proportional hazards description of the data when μ_1 is the only dose dependent parameter. At low and high doses fractionation reduced the effectiveness of gamma irradiation while, the fractionation of neutron produced results that were dependent on the dose range being examined. In the analyses of the data restricted to low neutron doses there was no change in the effectiveness of neutrons due to fractionation but when the entire dose range was included the results indicated that there was an increase in their effectiveness. The models that best describe the data for the entire dose range are much more complicated than those for the low doses. The Cox proportional hazards model fit the linear-quadratic term to the neutron exposures and the two-stage model indicates that both the initiation and promotion effects are needed to describe the carcinogenesis process following ionizing radiation exposure.

It remains to be determined how many of the recent advancements in the understanding of radiation biology are going to affect the issue of non-linearity in the low dose region of the dose response curve. The issue will in the future influence the approached to radiation protection.

Limitations

- A-bomb Data
    - Data available is grouped by city, sex, dose, age at exposure and calendar time; therefore we are correcting the average gamma and neutron dose and calculating the dose-dependent RBE based and the corrected average doses. If the corrected average dose moves up into the next dose group then the entire

group is moved up. As well, there is no variability associated with the average dose.

- The entire cohort is Japanese and exposed at one time. This reduces the ability to extrapolate the results to other populations from different times. Because there are genetic components of cancer risk, and cancer risk have been shown to change over time.
- There are uncertainties that are associated with the correction factors and methods that cannot be separated.

- JANUS Mouse Data
  - The study is retrospective therefore the data was collected with other studies in mind and we are using it to explore the effects of fractionation at low doses. Therefore we have to deal with the data that is available. There are not many truly low doses available in the gamma exposures. In fact the lowest dose available is 86 cGy for the single exposures and 100 cGy for the fractionated exposures. This means that any non-linearity that may occur at smaller doses (as seen in the A-bomb study at approximately 20 cSv) would be missed in these analyses. As well, the doses available did not permit us to explore the effect of radiation quality within the same sex. The gamma exposures were restricted to male mice and the neutron exposures were only female mice.
  - Could not look at possible trend with increasing fractionation because the 24 once-weekly exposure data did not contain data for low doses.
  - Inferences made about the mechanism of actions of an agent based on these analyses must be taken cautiously. Because although the two-stage model is

useful in generating hypotheses about the underlying mechanism of carcinogenesis, it has been shown that tumor incidence data does may not have the power to distinguish between initiating and promoting effects.

Future Work

- A-bomb Data
  - Analysis with data on the neutron activation measurements for a more accurate correction
  - Include Nagasaki to see if dose corrections for both cities bring the predictions of risk inline with one another. (Includes collection of copper samples in Nagasaki to allow for neutron activation measurements)
  - Use of individual data to for the dose corrections
- Mouse Data
  - Apply models to a data set that included comparable doses for both sexes and radiation qualities
  - Adjust the model to account for the fact that fractionated doses are distributed over time.